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(RESEARCH ARTICLE)

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Biologics for Moderate to Severe Asthma in Children From the department of Paediatrics at Masaka Regional Referral Hospital, UGANDA: A case series

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Abstract

Biologic therapies play a significant role in reducing exacerbations, hospitalizations and the need for maintenance systemic steroids, while also improving the quality of life in patients with severe asthma. The evidence for their clinical efficacy comes from randomised controlled trials (RCTs), extension studies, metanalyses and real-world data.Biologics offer significant benefits for managing severe asthma, particularly for individuals with type 2 inflammation, by reducing exacerbations, improving lung function, and enhancing quality of life, according to the ERS. These medications target specific inflammatory pathways involved in asthma, leading to improved control and reduced reliance on oral corticosteroids.

Keywords: Asthma; Children; Biologics; Uganda

1. Introduction:

Biologics are mostly large molecules, usually proteins, that serve as therapeutics. Biologics produced in vitro by recombinant technology are monoclonal antibodies. Targeted recombinant biological have been developed over the last 3 decades.

2. Methods

Two Children from the department of Paediatrics Masaka Regional Referral Hospital with Childhood onset Asthma are presented:

L.K 12yr male, known asthma patient for 4 years now on unknown inhaler medication presented with history of sudden chest pain described as heaviness, non-radiating associated with shortness of breath and wheezing. Reported history of restlessness in the night and failure to sleep. Mother reports that child was given 2 puffs of the inhaler which eased the patient's restlessness.

Report no history of cough, no hemoptysis. A diagnosis of Acute Asthma exacerbation was made. Child was treated with salbutamol Nebs and i/v Hydrocortisone. With resolution of symptoms.

N.h 3yr female presented with history of dry cough for 3 days, no associated chest pain, and no hemoptysis. A day prior to admission, child developed shortness of breath with audible wheezing. No associated chest pain or heaviness. A

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diagnosis of Acute Asthma exacerbation was made .She was treated with salbutamol Nebs and i/V Hydrocortisone. Discharged on salbutamol inhaler and oral prednisone for 3 days

3. Results

Many children in Uganda present with severe asthma according to GINA guidelines. Asthma may present in childhood. Moderate-to-severe asthma can generally be categorized by “type 2” inflammation and “non-type-2” inflammation.Th2 asthma is commoner.

Biologics are mostly large molecules, usually proteins, derived from living organisms and are indicated for moderate to severe asthma.

There are six FDA approved Biologics for Type 2 inflammation in severe asthma.

- Omalizumab-Anti IgE
- Mepolizumab-Anti IL5
- Resiluzumab-Anti-IL-5
- Benralizumab-Anti IL-5 receptor
- Dupilumab-IL-4 and Il-13 Inhibitor
- Tezepelumab-Anti TSLP

Three biologics, omalizumab, mepolizumab, and duplilumab, are FDA-approved for children as young as 6 years, whereas benralizumab and tezepelumab are approved for adolescents older than 12 years. All these agents reduce the rates of severe asthma exacerbations, whereas their effects on pulmonary function vary across age

4. Discussion

The development of monoclonal antibody therapies targeting specific components of the pathways relevant to asthma pathophysiology has revolutionized treatment of severe asthma both in adults and children and helped to further unravel the heterogeneity of this disease. However, the availability of multiple agents, often with overlapping eligibility criteria, creates a need for pragmatic guidance for specialists undertaking care of patients with severe asthma. In this review, we provide an overview of the data supporting the clinical efficacy of biologics in distinct asthma phenotypes/endotypes. We also focus on the role of biomarkers and treatable traits, including comorbidities, in the choice of asthma biologics, highlight which treatments have been demonstrated to be steroid sparing in corticosteroid dependent asthma, and provide practical guidance that can drive shared decision making on treatment choice with patients. In addition, we summarize what is known to date regarding long-term safety of these drugs, and lastly, discuss future directions in biologics research

4.1. Asthma Phenotypes and Endotypes

The model of asthma as a single entity has now been replaced by a much more complex biological network of distinct and interrelating inflammatory pathways. The term asthma is now considered an umbrella diagnosis for several diseases with distinct mechanistic pathways (endotypes) and variable clinical presentations (phenotypes). The precise definition of these endotypes is central to asthma management due to inherent therapeutic and prognostic implications.

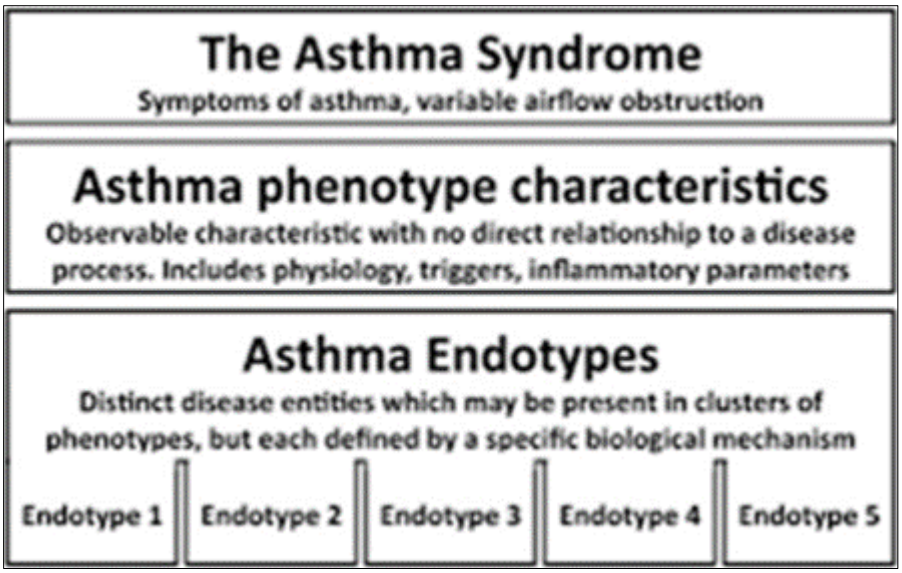

Figure 1 Asthma Phenotypes and Endotypes

Current advances in our understanding of the molecular mechanisms underlying airway inflammation have led to the development of monoclonal antibody therapies targeting these pathways, commonly referred to as biologics.

4.1.1. Anti-IgE therapy: omalizumab

IgE-mediated allergic asthma is a subset of T2-high asthma characterised by increased symptoms due to exposure to aeroallergens and represents roughly 70% of all asthma. The T2 cytokines, IL-4 and IL-13, promote class-switching of allergen-specific B-cells to produce IgE antibodies, which then bind tohigh-affinity receptors (FcεRI) on mast cells and basophils. Cross-linking of cell-surface IgE by the allergen results in cell degranulation, as well as the activation and release of pro-inflammatory mediators.

Omalizumab is a humanised, recombinant, monoclonal antibody (mAb) IgG1k that binds to the Fc fragment of IgE and reduces free IgE levels in serum, inhibits binding of IgE to FcεRI, and reduces FcεRI expression on target cells. It is currently approved for use in individuals 6 years and older and administered subcutaneously every 2 or 4 weeks. The dose is based on body weight and total serum IgE level (30–700 IU·m

4.1.2. Mepolizumab

Mepolizumab is a humanized mAb (IgG1k) that blocks IL-5's binding to the IL-5R expressed on the eosinophil and basophil cell surfaces. The US FDA approved subcutaneous mepolizumab ata dose of 100 mg every 4 weeks in 2015 for treatment of Severe Eosinophilic Asthma. Mepolizumab is currently approved for use in individuals 6 years or older. Mepolizumab is also approved for the treatment of CRSwNP, hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis.

4.1.3. Reslizumab

Reslizumab is a humanized mAb (IgG4k) that binds to IL-5. The US FDA approved intravenous reslizumab at 3.0 mg·kg−1 dose every 4 weeks in 2016 for the treatment of SEA. It is currently approved for use in individuals 18 years or older

4.1.4. Benralizumab

Benralizumab is a humanized afucosylated mAb (IgG1k) that targets the IL-5Rα expressed on eosinophils and basophils. The absence of fucose in the Fc domain facilitates binding to FcγRIII receptors on immune effector cells resulting in apoptosis of eosinophils via antibody-dependent cell-mediated cytotoxicity. The US FDA and the EMA approved benralizumab for the treatment of SEA in 2017 and2018, respectively. Benralizumab (30 mg) is administered subcutaneously every 4 weeks for the first three doses followed by 30 mg every 8 weeks. It is currently approved for use in individuals 6 years and older in the US and 18 years and older in the EU.

4.1.5. Anti-IL-4R therapy: dupilumab

IL-4 facilitates IgEisotype switching in B-lymphocytes, while IL-13 induces airway smooth-musclecontraction and upregulates nitric oxide synthase in bronchial epithelial cells, resulting in elevated FENO levels [2]. Dupilumab is a humanized mAb (IgG4) that inhibits both IL-4 and IL-13 signalling by binding to IL-4Rα subunit shared by IL-4 and IL-13 receptor complexes

4.1.6. Anti-TSLP therapy: tezepelumab

The airway epithelium, traditionally thought to function as a passive barrier, is now recognised to play anactive role as a central driver of early and dysregulated immune responses to external triggers such as infectious agents, allergens and pollutants. This results in a downstream inflammatory cascade through a group of epithelial cytokines known as alarmins, including TSLP, IL-33 and IL-25. These alarmins can serve as key therapeutic targets in both T2-high and T2-low asthma.

Tezepelumab is a human mAb (IgG2λ) that targets TSLP. The US FDA and the EMA approved tezepelumab for the treatment of severe asthma (regardless of T2 status) in 2021 and 2022, respectively Tezepelumab is currently approved for use in individuals 12 years and older. The recommended dose is 210 mg subcutaneously every 4 weeks.

5. Conclusion

Improved understanding of asthma's immunopathology has enabled the identification of specific biologic pathways and tailor treatments to individual phenotypes. The advent of biologic therapies has revolutionised the management of severe asthma. These therapies offer targeted, personalised treatment options that decrease reliance on systemic corticosteroids and improve patient outcome.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest is declared for this review article

Statement of informed consent

Not applicable as this was a review article

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