

THE USE OF BIOLOGICS IN THE MANAGEMENT OF SEVERE ASTHMA

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ABSTRACT

Biological therapies, often referred to as 'monoclonal antibodies', are becoming increasingly available for the management of asthma. These injectable therapies provide great hope for those with severe asthma not controlled by inhaled therapies and even by oral corticosteroids. The challenges, however, that are now faced as these therapies become more easily available, is to decide on who needs them and how best to use them as they will undoubtedly be very expensive. Each of these monoclonal therapies target a specific receptor or pathway. Broadly speaking, they can be divided into a few groups, namely: anti-IgE, anti-IL5, anti-IL13/4 and novel targets. Many different drugs are in various stages of development. Some have undergone clinical trials in other allergic conditions such as atopic dermatitis or eosinophilic syndromes. These indications are outside the focus of this asthma-focused review which will concentrate on the major drugs in development or those near to approval for the treatment of asthma.

INTRODUCTION

Asthma affects more than 300 million individuals worldwide with a prevalence of 10–15% in South Africa.¹ The most recent global asthma report ranks South Africa third in age-standardised mortality, although not in the highest strata of prevalence.¹ The reasons for the high mortality in South Africa are potentially multifactorial including poor access to medication, incorrect inhaler technique, tobacco smoking, over reliance on short acting beta agonists, and lack of prescription of inhaled corticosteroids. Notwithstanding these basic factors contributing to mortality, severe asthma is estimated to occur in 5% of asthmatics and to carry significant morbidity and mortality potential. Although multiple new combinations of inhaled steroids, long-acting beta-agonists and newer once-daily preparations, the development of biological therapies that directly target the underlying inflammatory pathways involved in asthma has been a great stride forward. Although costly, they do provide hope for those asthmatics who are uncontrolled on appropriate high-dose therapy (>500 ug fluticasone/>800 ug budesonide daily; Global Initiative for Asthma (GINA) step 5).

Before deciding on which new expensive medication to add to the patient's asthma treatment regimen, a careful evaluation of the whole patient is required. It is critical to ensure that the basics of asthma care have been covered and the disease managed correctly, as simple interventions may negate the need for biologicals. This review will cover the basic work-up for a 'potentially severe asthmatic', a review of what drugs are being developed and how each of them works. Which drug is

likely to be on the market or the most effective drug will not be reviewed. Given the unpredictability related to the availability and the specific indications in our setting, the focus will be the current evidence we have on the different agents.

WHAT IS SEVERE ASTHMA?

The international American Thoracic Society/European Respiratory Society (ATS/ERS) guideline on the definition, evaluation and treatment of severe asthma² promotes the following definition of severe asthma:

'Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma high-dose inhaled steroids and [long-acting beta-adrenoceptor agonist] LABA or leukotriene modifier/theophylline) for the previous year or systemic corticosteroids for >50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy.'

They define uncontrolled asthma as – at least – one of the following:

1. Poor symptom control: Asthma Control Questionnaire (ACQ) consistently >1.5, Asthma Control Test (ACT) <20 (or 'not well controlled' by the National Asthma Education and Prevention Program (NAEPP)/GINA guidelines).
2. Frequent severe exacerbations: two or more bursts of systemic corticosteroids (>3 days each) in the previous year.
3. Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year.

4. Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal).²

Prior to an asthmatic patient being regarded as 'severe', several key factors need to be reviewed that may make the patient

TABLE I: EVALUATING THE PATIENT WITH POTENTIALLY SEVERE ASTHMA

PRIMARY QUESTIONS	ISSUES TO CONSIDER
Is your diagnosis correct?	Is the history compatible? • Are there elements that you have overlooked? Have you documented reversible obstruction? • Peak flow variability >20% • Lung function FEV_1 , change 12% and 200 mL • Methacholine challenge Do you have supportive factors to support the diagnosis? • Immediate family history of asthma/atopy • Personal atopy or allergic symptoms • Raised FeNO, Eosinophils, IgE, etc
Are there environmental factors at play?	Cigarette smoking? • Primary • Second hand Air pollution? • Indoor/outdoor – diesel, dust, etc Occupational exposure? • Air pollutants • Chemical or allergens (flour, isocyanates etc) Allergen exposure? • Dust mites, cats, cockroaches etc • Fungi and moulds
Are there co-morbid diseases/factors?	Medications? • Aspirin • Non-steroidal anti-inflammatory medications • Beta-blockers Cardiovascular disease? • Valvular heart disease • Heart failure Metabolic disease? • Thyroid • Diabetes
Is the patient using the correct medication?	What have you prescribed? What have they received from the pharmacy? When last did they receive it?
Is the patient using the medication correctly?	What are they using? How often are they using it? How are they using it?

'difficult to control asthma' rather than 'severe asthma'. These are outlined in Table I below. Is your diagnosis correct? Are there factors that are making the asthma difficult to control? Either intrinsically such as obesity, heart failure, or are there extrinsic factors such as tobacco smoke exposure, air pollution or allergen exposure? The final aspects requiring review are: What asthma medication is prescribed, what is actually dispensed by the pharmacy and, finally, what and how it is used? The prescription of the 'best biological therapy' is pointless if the inhaler technique does not allow for adequate deposition of the inhaled steroid in the first place.

BASIC WORK-UP BEFORE DECIDING ON A BIOLOGICAL THERAPY

Subsequent to the review of the basic asthma diagnosis, medications and adherence to therapy, certain additional tests should be considered in the evaluation prior to biological therapy. Phenotyping is a current 'buzz' word and the approach to, and understanding of phenotypes, and what tests should be performed is continually changing at present. As a starting point, an IgE level, blood eosinophil count and, if available, a sputum smear and cell count (specifically looking for eosinophils), and a fractional exhaled nitric oxide (FeNO) test would be of value. For each of the biological therapies currently on the market or in development, certain cut-offs have been derived to assist in identifying who will benefit. There is no single definition of high or low eosinophils and some may not need an eosinophil count prior to treatment so these additional tests will be reviewed drug by drug. For a drug with a unique target such as Omalizumab, there is a table of doses for corresponding weight and IgE levels. It is therefore not possible to prescribe Omalizumab without knowing that the IgE level is within the prespecified range. Chest X-ray or CT scans could also be considered to rule out allergic bronchopulmonary aspergillosis (ABPA) or bronchiectasis and some of the new drugs in development, have potential impact on TB susceptibility so an interferon gamma-release assay (IGRA) or a tuberculin skin test (TST) might be required.

BIOLOGICAL THERAPIES FOR SEVERE ASTHMA

Table II below outlines the major biological therapies on the market and those nearing approval internationally. Others are also in early stages of clinical development, but this table includes those 'likely' to be seen on the local market. It is worth noting at this point in 2018 that Omalizumab (Xolair) is the only biological therapy for asthma on the market in South Africa. The

TABLE II: CURRENT MONOCLONAL ANTIBODIES FOR ASTHMA IN ADVANCED STAGE OF DEVELOPMENT

GROUPING	DRUG	COMPANY	TARGET/MECHANISM	PATIENTS & BIOMARKERS
Anti IgE	Omalizumab	Novartis	Free IgE antibody	Severe asthma atopic & serum IgE 30–700 IU/mL
Anti IL-5	Mepolizumab	GSK	IL-5 antibody	Severe asthma raised blood eosinophils >150 cells/ μ L
	Reslizumab	Cephalon	IL-5 antibody	Severe asthma on ICS+ LABA
	Benralizumab	Astra Zeneca	IL-5R α (receptor antibody)	High ICS; exacerbations; high blood eosinophils
	Lebrikizumab	Roche	IL-13	(Recently stopped further development)
	Tralokinumab	Astra Zeneca	IL-13	(Further development currently on hold)
	Dupilumab	Sanofi	IL-4R α (receptor antibody) also blocks IL-13	Mod-severe asthma with raised blood eosinophils
Anti TSLP	Tezepelumab	Astra Zeneca	TSLP	Mod-severe asthma, 'biomarker independent'

drug was launched internationally more than ten years prior to being marketed in South Africa. This is likely to have been a financial- and market-related decision rather than a lack of need or efficacy. Most reports suggest that less than 5% of asthmatics are truly severe, so the market for these drugs in a country such as South Africa is inevitably small and so we may not see them all available.

ANTI-IgE DRUGS

Omalizumab (Novartis) is registered both in the United States and South Africa as Xolair. It is a monoclonal antibody to circulating IgE. The primary studies were conducted nearly 20 years ago. The primary study was published in 2001 in the *Journal of Allergy and Clinical Immunology (JACI)*.³ Participants were required to be on moderate doses of inhaled steroids and have an atopy phenotype with positive skin-prick tests and an IgE level between 30 and 700 IU/mL. This requirement for the IgE level has remained as the drug is dosed at around 0.016 mg/kg IgE. A dosing table is required to ensure that the patient's weight and IgE level are appropriate for the dose to be given – if too overweight or too high IgE levels, the drug cannot be given. Several reviews have summarised the efficacy of Omalizumab in long-term follow-up. The Birmingham Regional Severe Asthma Service (BRSAS) reported an 80% reduction in exacerbations and 76% reduction in oral steroid dose from their registry.⁴

Xolair is currently available in South Africa and is an appropriate (albeit expensive) choice for severe asthmatics who have high IgE levels and fulfil the criteria for the weight-band dosing. The registered indications for Omalizumab are specific to an IgE body-weight chart. In the United Kingdom, for example, you may not prescribe the drug if the patient does not fit this chart, either by being overweight or having an IgE that is too high. Off-label usage is occurring in many settings with weight-IgE-inappropriate dosing. But given the cost of the drug, prescriptions should be as per registered indication only.

ANTI-IL5 DRUGS

There are two types of drug in this group: anti-IL5 antibodies (Mepolizumab and Reslizumab) and anti-IL-5 receptor antibodies (Benralizumab).

Mepolizumab (GSK) was the first registered in 2015 in the United States by the Food and Drug Administration (FDA) under the trade name Nucala. It is registered for use in patients over 12 years of age with eosinophilic type asthma. The primary registration study published in the *New England Journal of Medicine (NEJM)* in 2014⁵ demonstrated a 53% reduction in exacerbations using a subcutaneous injection monthly. Patients were required to have an eosinophil count of at least 150 cells per microlitre and be on high-dose inhaled steroids.

In 2016 Reslizumab (TEVA) was registered in the United States under the trade name CINQAIR. It demonstrated a 42% and 50% reduction in exacerbations in the two parallel studies performed for registration.⁶ Participants were required to have an eosinophil count of at least 400 cells per microlitre and be treated with medium to high dose inhaled steroids.

Benralizumab (AstraZeneca) was registered in the United States under the trade name Fasenra in 2017. It is registered for use in patients over 12 years of age with eosinophilic type asthma. This drug binds to the IL-5 receptor and results in removal of all eosinophils in circulation. Multiple registration studies were published in *The Lancet*.^{7,8} The SIROCCO study recruited patients with an eosinophil count of more than 300 cells per microlitre and on high dose inhaled steroids. This study showed a 45% reduction in exacerbations using a subcutaneous injection monthly.

ANTI-IL-13/IL4

There are two types of drugs in this group: anti-IL13 antibodies (Lebrikizumab and tralokinumab) and anti-IL4 receptor antibodies (Dupilumab). The early phase II studies of Lebrikizumab and Tralokinumab showed good promise, but, unfortunately, in the phase III studies the results were not sufficiently efficacious for the companies to take these drugs to market.⁹ (Lebrikizumab data not published.)

Dupilumab (Sanofi) is registered in the United States under the trade name Dupixent for eczema. It has been submitted for registration for asthma in 2018. This drug is a fully humanised IgG-4 monoclonal antibody that binds to the IL-4 α receptor and results in blockage of both IL-13 and IL4. The primary study to support registration was published in the *NEJM* in 2018.¹⁰ The study included patients over the age of 12 years with uncontrolled asthma on medium-to-high dose inhaled steroids. Overall the reduction in exacerbations was 54% but in those with high eosinophil counts it was 63%. A second study recruiting patients with oral steroids demonstrated a similar reduction in exacerbations and the ability to reduce steroid dose.¹¹

ANTI-TSLP

Tezepelumab (AstraZeneca) is an anti-thymic stromal lymphopoietin (TSLP), a cytokine that affects lymphocyte maturation via activation of antigen-presenting cells. TSLP expression is high in the airways of asthmatics. The blocking of cytokine regulates type 2 inflammation upstream to where the majority of the newer monoclonal antibodies target. The phase II data published in 2017 showed reductions in annualised exacerbation rates of more than 60% and it was not dependent on eosinophil count.¹²

Several other compounds are under investigation and new molecules and targets are continually being discovered.

In low-resourced settings, the use of biological therapies to treat the most severe patients will be severely restricted given the expected costs of these drugs. In selected patients the results can be dramatic in relation to exacerbations and the reduction in steroid requirements. This, however, does not constitute a cure or currently any option to reduce background medication (except maybe reducing oral corticosteroids). In future, though, a reduction in overall disease severity may occur, if control can be regained using these drugs and potentially long-term control of the disease requiring less medication. This currently remains a hope more than a reality from the currently published data.

CONCLUSIONS

Biological therapies for asthma provide hope for the most severe patients, although availability and affordability remain questionable. For all patients with severe asthma, the starting point should always be the basic steps described above, before prescribing an expensive medication. Confirming the disease, evaluating adherence and inhaler technique, excluding concomitant disease that may be exacerbating control and ultimately counselling on appropriate self-management and trigger avoidance are the basis for appropriate asthma management even when using expensive drugs such as monoclonal antibodies.

DECLARATION OF CONFLICT OF INTERESTS

David Masuku has no conflicts of interest. Dr Van Zyl-Smit has received honoraria for advisory board participation/academic presentations from: Aspen/GSK, Pfizer, Astra-Zeneca, Novartis, MSD, CIPLA and conducted clinical trials for Novartis, Astra Zeneca, GSK, Takeda, Merck, Almirall, Boehringer Ingelheim, Sanofi, Teva, Pearl, Pfizer, Roche and Genentech.

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