

Advances in the treatment of severe asthma

Fedoua Gandia and Sonia Rouatbi review current options. Article reproduced from our sister journal the *African Journal of Respiratory Medicine*

Asthma is a chronic inflammatory disease of the airways that affects over 300 million individuals worldwide.¹ For patients with severe asthma, which accounts for 5% to 10% of cases,² there is a need for improved therapies. In fact, patients with severe disease often fail to respond to conventional therapy, i.e. high doses of inhaled glucocorticosteroids in combination with long-acting β_2 -agonists (LABA),³ and can be associated with great morbidity and mortality as well as the accompanying health service and economic costs.⁴

Defining severe asthma

In 2010, the World Health Organization (WHO) defined severe asthma by the level of current clinical control and risks as 'Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children).' WHO's classification of severe asthma includes three groups, each carrying different public health messages and challenges: (1) untreated severe asthma, (2) difficult-to-treat severe asthma, and (3) treatment-resistant severe asthma (see Table 1). The last group includes asthma for which control is not achieved, despite the highest level of recommended treatment, and asthma for which control can be maintained only with the highest level of recommended treatment.⁵

1. Untreated severe asthma.
2. Difficult-to-treat severe asthma.
3. Treatment-resistant severe asthma. This group includes the following:
 - Asthma for which control is not achieved despite the highest level of recommended treatment: refractory asthma and corticosteroid-resistant asthma
 - Asthma for which control can be maintained only with the highest level of recommended treatment.

Table 1 WHO classifications of severe asthma

The American Thoracic Society (ATS) defined severe asthma on the basis of the identification of two major and seven minor criteria, of which at least one major and two minor requirements must be met for this diagnosis (see Table 2). These criteria have become the working definition of the National Heart, Lung and Blood Institute (NHLBI)

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Major criteria (must have one):

- Oral corticosteroids for >50% of past year.
- Continuous high-dose inhaled corticosteroids (ICSs). (ICS 1000 μ g fluticasone/beclomethasone)

Two of seven minor criteria:

- Concurrent use of at least one other controller medication.
- Daily symptoms requiring a short-acting inhaled β_2 -agonist.
- FEV₁ < 80% predicted.
- One or more urgent care visits in past year.
- ≥ 3 oral corticosteroid bursts in past year.
- Deterioration with decrease in corticosteroid dose of 25%.
- History of near-fatal event.

Table 2 Definition: ATS workshop, requires diagnosis and drug treatment of comorbidities (adapted from the American Thoracic Society)³

Severe Asthma Research Programme (SARP).³

According to the Global Initiative for Asthma (GINA) 2012, asthma severity is now by consensus classified on the basis of the intensity of treatment required to achieve good asthma control. GINA defined severe asthma as asthma that requires high intensity treatment to maintain good control, or where good control is not achieved despite high intensity treatment.¹

Prevalence and morbidity

A recent report from GINA estimated that asthma affects around 300 million people in the world.¹ In many regions of the world, notably Africa, there is a paucity of recent information on the epidemiology of asthma. The prevalence of asthma in the North Africa countries is moderate, but its impact is high. In 2009, prevalence was estimated at 3.45% in Algeria, 3.89% in Morocco and 3.53% in Tunisia.⁶ Prevalence was highest in children and older adults and in urban areas.⁶ A recent review suggests that prevalence is rising throughout sub-Saharan Africa, with rates from 5.7% to 20.3%, and highest in urban areas.^{7,8} South Africa's mortality rate of 18.5/100 000 asthmatics ranks fifth-highest in the world.^{8,9} As more Africans adopt Western lifestyles and move to urban centres, the current estimate of close to 50 million asthmatics living on the African continent is expected to grow.^{8,9} Asthma has an increasing impact on the health of Africans, especially in urban areas. Early diagnosis and proper management can significantly improve morbidity and mortality. It is therefore imperative to understand the mechanisms and factors associated with asthma and to treat it effectively.

Treatment of severe asthma

Current treatment of severe asthma

According to the current guidelines of the Global Initiative for Asthma, the National Asthma Education and Prevention Programme, and the British Thoracic Society, the treatment of patients with severe asthma consists of high-dose inhaled or oral glucocorticosteroids in combination with LABAs and/or additional controller medications such as theophylline, oral steroids, anti-IgE monoclonal antibody or leukotriene (LT)-antagonists.¹⁻³ Recommended treatment choices in order of introduction in the acute setting are:

- β_2 -agonists; inhaled by metered dose inhaler (MDI) or by nebuliser, or systemic (injected);
- anticholinergics; inhaled by MDI or nebuliser;
- corticosteroids; parenteral, oral, or inhaled.

Secondary treatment choices may include: theophylline (oral, parenteral), LT-receptor antagonists (oral), oxygen, and magnesium sulfate.¹⁻³

Stepwise treatment in acute asthma is summarised in Table 3.¹⁰

Biological agents

Several targets for treatment have been identified and multiple drugs are now under investigation. Most of these molecules are in advanced phases of research in order to find a place within the therapeutic arsenal.

Anti-IgE: omalizumab

The only biological agent licensed for the treatment of asthma is omalizumab. It is a recombinant humanised monoclonal antibody that binds to free circulating IgE with a subsequent reduction in the release of mediators of allergic reaction.¹¹ Several studies have confirmed that omalizumab treatment improves symptoms and reduces exacerbations in patients with allergic asthma that is not well controlled on high levels of asthma therapy.^{12,13} Omalizumab is currently the only biologi-

cal product approved for the treatment of asthma and specially the most severely ill patients. Its adverse effect profile is generally good.¹⁴

Anti interleukin-5 (IL-5): mepolizumab

IL-5 is central to eosinophil biology and increased in some patients with asthma. On the basis of these findings, its inhibition should be beneficial in asthma.¹⁵ IL-5 acts primarily in the peripheral blood and to a lesser extent in the airways.¹⁶ Conflicting results have been obtained. In fact, some studies with an anti-IL-5, mepolizumab, failed to show consistent evidence of clinical benefit in asthmatic patients.¹⁷ Others studies observed a significant improvement in asthma symptom scores, symptom control, and quality of life of these patients.^{18,19} Anti-IL-5 therapy may not provide benefit to all patients with severe asthma, but only to a subgroup with severe eosinophilic disease.

IL-4 and IL-13 inhibitors: altrakincept and pitrakinra

Altrakincept is a humanised recombinant protein. It is a soluble IL-4 receptor that captures the cytokine and prevents its binding to surface receptors and subsequent cell activation. Use of this agent is in the experimental phase.²⁰ The role of IL-4 and IL-13 blockers in the treatment of severe asthma will emerge over the next few years.

Pitrakinra is a recombinant protein that binds to IL-4R α , reducing allergen-induced late responses with few adverse events. Various clinical trials on severe asthma indicated its efficacy in reducing bronchial hyperreactivity.²¹

Inhibitors of tumour necrosis factor: golimumab and etanercept

Other targeted treatments, such as tumour necrosis factor (TNF)- α blocking agents (golimumab²² and etanercept²³ have shown beneficial effects on exacerbation

<p>A. First line</p>	<p>Oxygen: by 40% facemask or nasal cannulas to keep saturation >92%. SABAs: via nebuliser (5 mg salbutamol or 1 mg fenoterol in premixed UDVs) every 20 minutes until a satisfactory response; or via MDI plus LVS (10–20 puffs (100 μg/puff) over 20 minutes, taking several deep breaths from spacer after every two puffs). Systemic corticosteroids: prednisone 0.5–1 mg/kg orally stat and daily; or hydrocortisone (or equivalent) 100–200 mg intravenously (IV) 6-hourly in severe acute asthma or if unable to swallow or if vomiting. These treatments are usually administered concurrently to achieve the most rapid resolution of the attack and prevention of relapse.</p>
<p>B. Second line</p>	<p>Ipratropium bromide: 4-hourly via nebuliser (0.5 mg in premixed UDVs, usually with a SABA) every 20 minutes until a satisfactory response; or via MDI plus LVS (up to 20 puffs (20 μg/puff) over 20 minutes, taking several deep breaths from spacer after every two puffs)</p>
<p>C. Third line</p>	<p>Intravenous magnesium sulfate: 1–2 g infusion over 20 minutes. Intravenous aminophylline: loading dose of 5 mg/kg infusion over 30 minutes (administer half the dose if on maintenance theophyllines), then maintenance infusion of 0.5 mg/kg/h.</p>
<p>D. Fourth line</p>	<p>Intravenous salbutamol: 0.25 mg IV slowly, then maintenance infusion of 3–20 μg/min.</p>
<p>Notes: SABAs = short-acting inhaled β_2-agonists; UDVs = unit dose vials; MDI = metered dose inhaler; LVS = large-volume spacer.</p>	

Table 3 Stepwise treatment of acute asthma¹⁰

rate, but not on lung function in the subgroups of adults with severe asthma.

IL-2 inhibitors: daclizumab

Daclizumab is a humanised IgG1 monoclonal antibody against the IL-2R chain of activated lymphocytes. This agent showed improvement in pulmonary function and asthma control in patients with moderate to severe chronic asthma. The mechanism of action involves inhibition of pro-inflammatory cytokine generation by IL-2R blockade in activated T-cells.²⁴

Inhibition of chemokines

Epithelial eotaxin-2 and 3 are increased in asthma and severe asthma.²⁵ They have a chemotactic effect on eosinophils. Because so many cytokines are involved in asthma, drugs that inhibit the synthesis of multiple cytokines may prove to be more useful. In addition, the risk of side-effects with these non-specific inhibitors may be reduced by inhaled route delivery.²⁶

Non pharmacological 'targeted' treatment

Bronchial thermoplasty

Bronchial thermoplasty is a new bronchoscopic therapeutic procedure to improve control of moderate-to-severe asthma by reducing the mass of airway smooth muscle and attenuating bronchoconstriction.^{27,28} This procedure has been approved by the United States Food and Drug Administration for routine clinical use and has been shown to reduce the frequency of asthma exacerbations and improve asthma control so that pulmonary function remains stable over a period of 5 years.²⁹ Therefore, this technique might be an option for patients not responding to ordinary medication. However, additional studies are needed to establish accurate phenotype of positive responders, durability of the effect, and long-term safety.

High-altitude treatment

High-altitude treatment in asthma has been used before, and its benefits have been attributed to the lower allergenic load, particularly reduced exposure to house dust mite, present at high altitudes. This treatment improves clinical and functional parameters, and decreases oral corticosteroid requirement in patients with severe refractory asthma, irrespective of allergic sensitisation.³⁰ A periodic rehabilitation programme at high altitude might be a good treatment for patients with severe refractory asthma.

Conclusion

Although, patients with severe asthma represent 5% to 10% of all asthmatics, they have the greatest unmet treatment needs, and they are the group that requires novel treatment approaches. Asthma has an increasing impact on the health of Africans, especially in urban areas. Early diagnosis and proper management can significantly improve morbidity and mortality. The identification of innovative therapies that are safe and effective and target sub-phenotypes of asthma is of great importance. Genotypic and phenotypic factors are important to guide the choice of intervention in each patient with

severe asthma. Phenotyping the severe asthma patient is essential to ensure the right treatment is given to the right patient allowing for better asthma control and better quality of life.

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