Breathing Easier – Advances in Asthma

by Dr. John A. O’Brien, Gen Re, Cape Town

In all fields of science and medicine, there is an explosion of new information. When contemplating what is new in asthma the temptation is to focus only on new developments – information regarding pathways of inflammation or potential products that may modify the asthma disease process. However, as recent years have seen few new treatments become available, it is more beneficial to focus on the progress in understanding asthma and how the treatment has changed with time. Despite the availability of effective treatments, the control of many individuals’ asthmatic condition remains sub-optimal, and this has a significant impact on their school and workplace attendance and performance.

What is asthma?

“Asthma is one of the most common chronic diseases, with an estimated 300 million individuals affected worldwide. Its prevalence is increasing, especially among children” according to the Global Initiative for Asthma (GINA), which was launched in 1993 in collaboration with the National Heart, Lung, and Blood Institute, National institutes of Health, and the World Health Organization. This major initiative is being undertaken to improve knowledge about and the standards of care of asthma and to produce guidelines for clinicians and information for patients.

Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

The typical young asthmatic presents with episodes of bronchospasm and complains of wheeze, tight chest, difficulty breathing and cough. There is no question that spasm of the smooth muscle in the airway is a major cause of these symptoms, but it is crucial to realize that this is secondary to airway inflammation.
How large is the problem?
GINA commissioned the Global Burden of Asthma report, published in 2004, which estimated that approximately 300 million people worldwide have asthma. In 2001 asthma was ranked the 25th leading cause of disability-adjusted life years (DALYs), representing the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. It is now estimated that asthma accounts for 15 million lost DALYs per year – a level similar to diabetes, cirrhosis of the liver or schizophrenia.

Asthma accounts for approximately one in every 250 deaths worldwide. Therefore, with the development in the understanding of the pathogenesis of asthma and the role of the available medications came the realization that asthma appeared to be becoming more common and possibly more severe. Explanations for this have been sought, and the numerous theories include increased urbanization.

With the proportion of the world’s population that is urban projected to increase from 45% today to 59% in 2025, there is expected to be a marked increase in the number of asthmatics. It has been projected that by this date there may be an additional 100 million. Other causal factors include pollution, obesity and smoking although current theory suggests that different factors may be responsible in different social environments. For example, in Eastern European countries infection, diet and pollution have been identified as contributing factors while in the U.S. inner city population poverty, allergens and stress may all contribute.

In affluent societies potential triggers and aggravators include smoking, air pollution and obesity, family size and even children’s day-care facilities. It has long been known that obese asthmatics are more difficult to treat; conventionally this has been ascribed to increased thoracic and abdominal fat causing pressure on the airways. There is now evidence that the adipose tissue itself is metabolically active and produces mediators that act on the airways. Obesity not only complicates asthma but can be causal.¹

Treatment of asthma
Treatments in the first part of the 20th century focused on medications designed to relieve airway smooth muscle spasm. Some early suggestions for treatment look surprising today as they included smoking medicated “anti-asthma” cigarettes and inhaling the fumes of combustible powders with such ingredients as tobacco, potash and plants.² The presence of inflammation in the airway of asthmatics has been recognised for many years. With the development of oral corticosteroids, many asthmatics were placed on cortisone. As a powerful anti-inflammatory this worked well to control asthma and emphasised the importance of airway inflammation in the pathogenesis or cause of asthma. However, the improved control came at a price, as systemic corticosteroid has a number of predictable side effects, including skin fragility, weight gain, osteoporosis, glucose intolerance and a number of others.

In the early 1970s inhaled corticosteroids first became available, offering significant advantages. The corticosteroid dosage was now measured in micrograms (µg) and could be delivered directly to the site of inflammation in the airways. These new products dramatically reduced the need for asthmatic patients to receive oral steroid therapy. Side effects from the inhaled steroids are minimal. Inhaled steroids were first introduced with a low dosage of 50 µg requiring users to take two puffs four times a day. Adherence to this type of regime was clearly difficult and the next advance was the development of higher dose preparations – inhalers of 100 µg and 250 µg with use frequency reduced to twice daily, which is quite acceptable to most patients.

Apart from the inhaled steroids, few medications were available. Patients continued to rely on short-acting beta₂-agonist bronchodilators and there was widespread use of the oral theophyllins. The latter medication is used far less frequently today due to the narrow therapeutic balance between its beneficial effects and the side-effects. It is held that they act as bronchodilators but perhaps do have mild anti-inflammatory effects as well.
The next major advance was the development of long-acting inhaled beta₂-agonist bronchodilators — medications that work to relax the muscles surrounding the airways — but the development of these drugs was dogged by safety concerns. In the late 1970s and early 1980s there were epidemics of asthma deaths and analysis pointed to a link with beta₂-agonist treatment. It was not clear initially if the product itself was toxic or whether an excess use of bronchodilators was itself a marker of asthma severity, meaning the deaths were the result of the poor assessment by clinicians and poor management by patients.

This controversy still exists although it is now generally accepted that both types of beta₂-agonists — short-acting and long-acting — are safe if used in conjunction with inhaled corticosteroids. To emphasise this point the U.S. Food and Drug Administration marks long-acting beta₂-agonists with a “black box” warning that indicates they should not be used alone for the treatment of asthma.

**How successful is the treatment?**

The frightening information regarding asthma mortality triggered an era of international asthma education with the intent of ensuring that patients and care givers had a better understanding of the disease and were appropriately informed and counselled so that they could react appropriately if there were any deterioration in patients’ conditions. The standard of treatment in the 1970s and 1980s was increased doses of inhaled steroid driven by symptom severity. Indeed, this proved effective and with robust endpoints, such as asthma deaths, correlation could be drawn between the number of canisters of inhaled steroids used in a year and the risk of asthma.

However, not all patients achieved optimal control using inhaled steroid alone, prompting the question whether it was better to continue to increase the dose of inhaled steroid or to add additional treatment, in particular the relatively new class of agents, long-acting beta₂-agonist inhalers. A number of studies were performed which overwhelmingly confirmed the fact that adding a long acting beta₂-agonist to an inhaled steroid was a more effective intervention than simply increasing the dose of inhaled steroid.3 Because this blend of medication was so effective, the large pharmaceutical companies began to produce combination inhalers designed for use just twice a day, a development that revolutionised asthma treatment allowing the vast majority of asthmatics to become well controlled.

Around this time a number of worldwide studies indicated that the general standard of asthma control was disappointingly poor despite the apparent availability of good medications. Indeed in the early 1990s, a pharmaceutical firm ran an art competition for young asthmatics and asked them to paint what their asthma represented to them. A number of horrifying images like the ones used to illustrate this article emerged.

The asthma guidelines produced by numerous national and international bodies stressed the assessment of severity as the starting point for the initiation of appropriate treatment. Difficulties in using these guidelines arose as clinicians sought to slot patients into severity grades when they were already receiving treatment. The guidelines did, however, serve the purpose of ensuring the severity of asthma was not underestimated.
Table 1 – Levels of asthma control (adapted from GINA guidelines)\(^5\)

<table>
<thead>
<tr>
<th>Daytime symptoms</th>
<th>Controlled</th>
<th>Partly controlled</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Twice or less per week</td>
<td>More than twice</td>
<td>3 or more features of partly controlled asthma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity limitation</th>
<th>None</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night time symptoms</td>
<td>None</td>
<td>Any</td>
</tr>
<tr>
<td>Rescue treatment</td>
<td>Twice or less</td>
<td>More than twice</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal</td>
<td>&lt;80% predicated</td>
</tr>
</tbody>
</table>


Table 2 – Impact of asthma on work school and home activities in past four weeks

<table>
<thead>
<tr>
<th></th>
<th>Not well controlled</th>
<th>At least well controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the time</td>
<td>3.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Most of the time</td>
<td>10.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Some of the time</td>
<td>27.3</td>
<td>1.4</td>
</tr>
<tr>
<td>A little of the time</td>
<td>33.7</td>
<td>18.7</td>
</tr>
<tr>
<td>None of the time</td>
<td>25.4</td>
<td>79.8</td>
</tr>
</tbody>
</table>

Numerous studies compared the two combination inhalers and the various inhaled steroids on the market. These were mostly commercially driven and designed to show the superiority of one product over another. When the studies were re-analysed with a different intention, however, it was demonstrated that even in a closely monitored and supervised study situation a surprisingly small number of patients achieved good control. It was recognised that while the treatment of conditions such as hypertension and diabetes were guided by clear end points; the control of blood pressure and of glucose levels, the treatment of asthma was often not pursued to the point of achieving optimal control. In other words, as long as the patient was on treatment and not complaining, therapy was considered adequate.

The Gaining Optimal Asthma Control (GOAL) study was one of the landmark investigations looking for optimal asthma treatment.\(^4\) In this study subjects entered with varying severity and treatment regimens but had their treatment increased over the course of a year until they achieved optimal asthma control or reached maximal therapy. In order to qualify as “totally controlled” the subjects health had to reflect the following:

- No daytime symptoms
- No use of rescue beta\(_2\)-agonist
- No night time symptoms, exacerbations or emergency room visits
- An objective measurement of peak flow at greater than 80% of predicted

To be “well-controlled” required minimal symptoms and no markers of severity, such as the emergency room visits. The medical profession has recognised over the last 10 to 15 years that for asthma to be adequately controlled the symptoms must be controlled and lung function optimised so that the asthma interferes as little as possible in the daily lives and activities of asthmatics, including school, sport and work.

The approach of modifying treatment progressively until optimal control is achieved prompted change to many international guidelines, including those of GINA. The emphasis is now on assessing control rather severity alone, so that the condition of asthmatics is classified as well-controlled, partially controlled or poorly controlled (Table 1). An asthmatic with severe disease that is well-controlled may now be contrasted with a mild asthmatic with poor control.

There are well-validated simple asthma control questionnaires that can be used to assess the level of control. These together with objective measurements of lung function can be used to guide and modify treatment. The 2006 European National Health and Wellness Survey showed that a large proportion of asthmatics had uncontrolled asthma. A follow-up in 2008 estimated asthma prevalence and control in five European countries.\(^6\) The prevalence of self-reported physician diagnosis of asthma was 6.1%. In treated asthmatics 18 years and older, 56.6% were found “not well controlled” when using the five-question, self-completed asthma control test (ACT).\(^7\) The study also looked at the impact of asthma control and found subjects with asthma that was “not well-controlled” suffered significant interference with their work, school and home activities compared to those who were “at least well-controlled” (Table 2).
It is established that, even in countries with well-developed health systems, asthma control is suboptimal in many cases. This is despite the availability of medications that promise control of the disease with minimal or no side effects. So why should we be doing so badly?

It is the nature of asthma to cause symptoms so it is natural that patients will determine their treatment by the presence of symptoms rather than commit to regular preventative treatment. In conditions that are not symptom-driven, such as hypertension, patients will take the medication regularly in order to reduce the likelihood of poor long-term outcomes. Many asthmatics need to be convinced that poor control of asthma has the potential to lead to fixed airway obstruction and adverse outcomes, including acute deteriorations and hospitalisation and even death.

Commonly, there is non-adherence to medication regimes, a tendency for people to “deny” their disease and to resist inhaler therapy. Some favour taking tablets, feeling that using an inhaler reinforces the presence of their disease – a constant reminder to themselves as well as others. Many such problems, including poor inhaler technique, can be overcome with appropriate education and support that encourage patients to use objective outcome measures, including lung function, control questionnaires and action plans, if their symptoms escalate.

It is difficult to control an inflammatory airway disease in people who continue to smoke. Emotional factors and stress can also lead to poor control. Doctors must be alert to other contributing and aggravating factors, such as upper airways allergy, sinusitis and gastrointestinal reflux. Although most combination inhalers are prescribed for use twice a day, it is not uncommon for one dose to be omitted. Once-a-day combination inhalers will soon be commercially available, which should prove beneficial in this respect.

What new treatments are available?

Improved understanding of different inflammatory pathways in asthma has prompted investigation of the potential for treating it using biological agents.

The sole available product of this type is an anti-IgE antibody drug Omaluzimab (Xolair). IgE is the antibody pivotal to the allergic reaction and its activation releases many inflammatory mediators. In theory, by blocking IgE the inflammatory pathway is aborted. Omaluzimab works by binding to IgE when it is released and inactivating it. Antibody to IgE is produced in a murine model before being humanized and given by subcutaneous injection every two or four weeks. The product has shown most success in reducing exacerbations in severe asthmatics who have elevated IgE, but its cost means widespread use has been limited.

With long-standing severe asthma, hyperplasia and hypertrophy of the airway smooth muscle can take place. A bronchoscopic technique known as bronchial thermoplasty has been introduced. A bronchoscope is inserted into the airway and a current is applied via an endobronchial catheter. This causes regression of bronchial smooth muscle and perhaps modifies the asthma process by other mechanisms including denervation. The results of this technique have now been followed for five years or more. The technique appears to show promise in severe asthmatics by reducing exacerbation rates but has little effect on improving lung function. Cost once again is a significant limiting factor and patient selection is important as experience with the technique continues.

Asthma is already common and is set to become more so. Despite the availability of effective medications, the asthmatic condition of a surprisingly large number of individuals remains poorly controlled. This has significant impact on their performance and indeed asthma is potentially fatal. In the assessment of an asthmatic, both severity and adequacy of control are important. Control can be assessed by asthma control questionnaires and lung function. The medications used to treat asthma are generally safe with minimal or no side effects or complications. The one exception is oral corticosteroid which is seldom required as maintenance treatment today and would be reserved for only the most severe asthmatics.
Endnotes


About the Author

Dr. John O’Brien is the CMA for Gen Re in South Africa. He is a pulmonologist in practice in Cape Town. He is a past president of the South African Thoracic Society and is on the editorial committees for the South African Thoracic Society guidelines for asthma and COPD. He has been a clinical investigator in more than 70 clinical trials in asthma and COPD. Tel. +27 21 412 7700 or john.obrien@genre.com.