UNIT NO. 4

AN UPDATE ON STRATEGIES IN THE MANAGEMENT OF ASTHMA

Dr Kong Po Marn

ABSTRACT

While the treatment guidelines are very useful, newer understanding is continually emerging that may eventually alter the management strategy in asthma. Recent studies have questioned the use of continuous inhaled steroids in mild asthma, the use of single inhaler treatment with combination inhaled steroids and long acting beta-agonist, the use of exhaled nitric oxide, monoclonal antibodies against IgE, as well as exploring future modalities that may alter the treatment guidelines in the future. This is a short review of some of these studies.

SFP2006; 32(4): 18-20

INTRODUCTION

The introduction of management guidelines has helped to standardise the management of asthma to a large extent. The GINA guidelines[1] in particular have helped make asthma treatment more uniform internationally and its frequent updates include reviewing the latest relevant literature. However, as is common is most aspects of medicine, new ideas and concepts take years, even decades, before it becomes common practice. As the GINA guidelines have been discussed elsewhere, the topics reviewed here will deal with either aspects of standard asthma management not currently dealt with in the guidelines or developments that are likely to impact the frontline of asthma management. These topic reviews certainly do not suggest deviating from practice guidelines, unless done after serious consideration and expert opinion.

INHALED CORTICOSTEROIDS

Inhaled corticosteroids (ICS) is the most important agent in asthma management. The GINA guidelines advocate using them regularly in all patients except those with mild intermittent asthma. Their benefits in reducing morbidity and mortality have been well documented. However, recent studies appear to challenge this recommendation with regard to patients with mild asthma and will perhaps offer an alternative treatment strategy.

Combination treatment with ICS and long acting beta-agonists are relatively recent additions to the armamentarium. They have shown great benefit, but their role is still not completely defined. Different ways of adjusting dosages offer new and potentially more effective control.

KONG PO MARN, Consultant, Department of Respiratory Medicine, Tan Tock Seng Hospital

MILD ASTHMATICS

The management of mild asthmatics presents more challenges that it would seem. These are patients who have minimal reported symptoms and some are not prescribed ICS as per guidelines, yet studies have shown that they have an unexpectedly high rate of exacerbations[2]. It is also suspected that compliance with ICS is low even when prescribed because of a feeling of wellness.

The IMPACT trial[3] (Improving Asthma Control) was conducted to see if intermittent use of ICS in conjunction with an asthma action plan could be an alternative. This study recruited only adults with mild persistent asthma. Two hundred and twenty-five subjects were randomised and 199 completed the study. The study had 3 arms that compared patients on regular Budesonide, regular zafirlukast and a group with no regular preventer medication. The primary outcome studied was morning peak flow. Patient were all given a plan of action if symptoms worsened and the group with no regular ICS took ICS when needed, according to the treatment plan.

The study found no significant difference in the morning peak flows, exacerbations, quality of life scores, or lung function. However, there were more symptom-free days and lower level of inflammatory markers in the group on regular budesonide. This study offers an option of treating mild persistent asthma that may more accurately reflect real life practices. One important aspect of this study is that it shows the effectiveness of a patient directed treatment plan. However, care should be exercised and that the cohort of patients has stable mild asthma, as seen by the symptoms, as well as the low levels of inflammatory markers.

The OPTIMA[4] trial is another large, multicenter trial that adopts a different approach. The cohorts of subjects are different. They included mild asthmatics not on ICS or less than 400 mg/d of inhaled budesonide and included smokers. Subjects not previously on ICS were given budesonide or budesonide plus formoterol, a long acting beta-agonist (LABA). Subjects previously on steroids were randomised to budesonide 200mg/d, budesonide 200mg/d plus formoterol, budesonide 400mg/d and budesonide 400mg/d plus formoterol. The outcome was that adding inhaled steroids in those not previously on ICS reduced risk of severe exacerbations but formoterol only improved lung function. However, for those already on ICS, adding formoterol was more effective than doubling ICS.

While these two studies appear to contradict each other, they cannot be directly compared as the cohorts are different. However, they would suggest that steroids may be important in mild asthmatics, but timing the dosing correctly may also be crucial.

COMBINATION TREATMENT IN MODERATE TO SEVERE ASTHMATICS

The use of combination treatment with ICS and LABA in moderate to severe asthma is clearly proven to be of benefit and has now formed the mainstay of treatment in moderate to severe asthma[5]. Studies such as GOAL[6] have shown that a large proportion of asthmatics can be controlled well although larger amounts of drugs are needed.

While regular maintenance therapy is the usual regimen, the use of formoterol/budesonide allows for a single inhaler to act as preventer and reliever while at the same time titrating inhaled steroids. The study by O'Byrne et al[7] examined the hypothesis that using combination budesonide/formoterol as a reliever medication instead of a short acting beta-agonist (SABA), would decrease exacerbations. This was a large study with 2,760 patients randomised and included paediatric patients. The study indeed showed a 45 to 47% decrease in exacerbation as compared with using SABA as reliever therapy. This represents yet another possible strategy for management of such asthmatic patients. It should be noted that symptom control was not very good although that was not the primary outcome studied. This study again highlights that timing the increase of ICS may be important.

EXHALED NITRIC OXIDE

The diagnosis and monitoring of asthma control has been dependant on tests of airway hyperresponsiveness or spirometry (as according to guidelines). It has also been appreciated that these tests do not correspond very well with inflammation, nor do they correlate well with treatment. Tests of airway inflammation have until recently depended on bronchoscopic studies of the airway and these are not generally available at short notice and are invasive.

The search for a non-invasive marker of airway inflammation has included eosinophils in induced sputum as well as exhaled markers. Gases such as nitric oxide (NO), carbon monoxide, exhaled polycyclic hydrocarbons, as well as chemicals extracted from breath condensates have all been studied. Among all these, exhaled nitric oxide (FE_{NO}) has shown the most promise.

NO was first detected in exhaled air in 1991. It is produced throughout the respiratory tract and collection and measurement was tedious. However, the protocols for collection are now standardised[8] and machines, such as the Minox, are becoming smaller and portable. It is currently even feasible to measure FE_{NO} in intubated patients.

Exhaled NO has been extensively studied. It has been shown to be more sensitive than standard tests for asthma, especially when combined with sputum eosinophils[9]. It is also useful in monitoring management as it responds rapidly to steroids[10]. It has also been shown to predict steroid responsiveness[11]. However, it is its use in titrating asthma treatment that will likely show its usefulness in the clinics.

Two studies are of particular clinical interest. Smith et a[12] used FE_{NO} to titrate ICS use in an adult cohort with mild to moderate asthma. They concluded that ICS use was much lower than that of the control group who were titrated according to the GINA guidelines. Additionally, FENO was found to predict those who responded to ICS. In a similar study among paediatric patients[13], the steroid use did not differ among those titrated with FE_{NO}, but the FEV1 and bronchial hyperresponsiveness improved.

FE_{NO} has shown that it has clinical applications and adds to asthma management. It does suggest that the "one dose fits all" practice may be suboptimal. Again, it may be its ability to allow us to accurately pick up an exacerbation and start timely intervention that may lead to better control.

ANTI-IgE

IgE is crucial to the inflammatory process seen in allergic conditions such as asthma and allergic rhinitis. Once IgE is crosslinked with its receptors, the complex can cause the release of histamine and trigger an immediate reaction. A second response triggered by other mediators occurs about 1 hour after the initial event. Because of the central role of this mechanism in asthma, as well as other allergic diseases, it had been hypothesised that a highly specific monoclonal antibody to block this process could help improve asthma control.

Omalizumab is a humanised monoclonal antibody that binds to the receptor-binding portion of the IgE and hence, prevents linkage. It can only bind IgE that is in circulation. It is administered parenterally and the patients would usually need to come to the clinic every 2 to 4 weeks. Dosage needs to be individualised according to body weight and serum IgE levels.

Although this has been studied since the mid 1990s, it is only in the last few years that phase 3 trials have been performed. These trials were on patients with severe asthma (INNOVATE etc) and not controlled on high dose ICS and LABA. The treatment reduced mild and severe exacerbations and improved quality of life[14,15].

The drug holds promise for the group of patients who are difficult to manage with conventional treatment. However, the cost is currently prohibitive and its use would mostly be in a specialist setting for now.

FUTURE MODALITIES

Anti-TNF-a

Refractory asthma involves a small proportion of asthmatics, but contribute a disproportionate morbidity and mortality rate. Such patients tend to be on nearly all available standard therapies and are still symptomatic. Their pathology is also different from patients with milder asthma. They tend to have greater neutrophilic involvement and airway remodelling. Treatment options are usually limited and they remain symptomatic.

TNF-a is expressed by mast cells in inflammation and are detected in increased amounts in the bronchoalveolar lavage fluid of severe asthmatics as compared with patients with milder asthma. As such, it constitutes a new modality that could potentially affect the inflammation in asthma positively. Available antagonists are currently already in use for the treatment of autoimmune disease like rheumatoid arthritis.

Berry et al[16] performed a study that compared patients with mild asthma, severe asthma and a group of health controls. They found that patients with refractory asthma had increased expression of TNF-a. In the trial that was performed, the subjects were given eternacept and it was found that the bronchial hyperresponsiveness decreased and the asthma related quality of life improved. A second study in moderate asthmatics decreased exacerbations.

However, in our local context, the prevalence of TB makes careful patient selection important. Nevertheless, in a group of patients with such a severe condition, an additional therapeutic modality is useful.

Interferon-b (IFN-b)

Asthma exacerbations are most commonly viral which leads to lower airway inflammation. The most common agents are the rhinoviruses. Asthmatics are known to be more susceptible to such infections. After a viral infection, rapid cell death (apoptosis) of the infected cells is an important anti-viral response and this is believed to be mediated by IFN-b.

A study by Wark et al[17] recently showed that viral production, as measured by the RNA was significantly greater in the infected bronchial epithelial cells (BEC) of asthmatics compared to those of a normal subject. This was due to less effective apoptosis in asthmatic BEC. IFN-b was also produced in lower amounts. Addition of IFN-b led to increased apoptosis of infected asthmatic BECs. This would suggest that IFN-b, which is already commercially available, could potentially be useful as a therapeutic agent.

REFERENCES

1. Global Initiative for Asthma. Global strategy for asthma management and prevention: NHLBI/WHO workshop report. Updated 2004. Bethesda, Md.: National Heart, Lung and Blood Institute, 2004.
2. Turner-Warwick M. Nocturnal asthma. A study in General Practice. J r Coll. Gen Pract 1989; 39:239-43.
3. Boushey HA, Sorkness CA, King TS et al. Daily versus as needed corticosteroids for Mild Persistent Asthma. N Engl J Med 2005; 352: 1519-28.
4. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R et al. Low dose inhaled budesonide and formoterol in mild persistent asthma. The OPTIMA randomized trial. Am J Respir Crit Care Med. 2001; 164:1392-7.
5. Pauwels RA, Lofdahl C-G, Postma DS. Effect of inhaled formoterol and budesonide on exacerbation of asthma. N engl J Med 1997; 337: 1405-11.
6. Bateman EA, Boushey HA, Bosquet J. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. Am J Respir Crit Care Med. 2004; 170:836-44.
7. O'Byrne PM, Bisgaard H, Godard PP. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J resp crit Care Med 2004; 171:129-36.
8. Recommendation for standardized procedures for the online and offline measurement of lower respiratory nitric oxide and nasal nitric oxide in adults and children, 2005. Am J Respir Crit Care Med 2005; 171:912-30.
9. Smith AD, Cowan JO, Filsell S. Diagnosing asthma. Comparisonn between exhaled nitric oxide measurements and conventional tests. Am J Respir crit Care Med 2004; 169:473-8.
10. Jones Sl, Kittleson J, Cowan JO. The predictive value of exhaled nitric oxide measurements in assessing change in asthma control. Am J Respir Crit Care Med 2001; 164:738-43.
11. Smith AD, Cowan JO, Brassett KP. Exhaled nitric oxide. A predictor of steroid response. Am J respir Crit Care Med 2005; 172:453-9.
12. Smith AD, Cowan JO, Brassett KP. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005; 352:2163-73.
13. Pijnennburg MW, Bakker EM, Hop WC. Titrating steroids on exhaled nitric oxide in children with asthma. Am J Respir Crit Care Med 2005; 172:831-6.
14. Humbert M, Beasley R, Ayres J. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005; 60:309-16.
15. Bosquet J, Cabrera p, Berkman M. The effect of treatment with omalizumab, an anti IgE antibody, on asthma exacerbationa and emergency medical visits in patients with severe asthma. Allergy 2005; 60:302-8.
16. Berry MA, Hargadon B, Shelley M. Evidence of a role of tumour necrosis factor a in refractory asthma. N Engl J Med 2006; 354:697-708.
17. Wark PAB, Johnston SL, Bucchieri F. Asthmatic bronchial epithelial cells have a deficient innate immune response too infection with rhinovirus. J exp Med 2005; 201:937-47.

LEARNING POINTS

- **Treatment of asthmatic patients will benefit from individualisation. Future data may alter current treatment recommendations.**
- **Self-directed asthma treatment plans can give beneficial outcomes.**
- **Timing intervention accurately to prevent exacerbations may become more important as monitoring modalities like FE_{NO} become more convenient.**
- **Other aspects of asthma pathophysiology like Anti-TNF-a and Interferon-b (IFN-b) may offer alternative intervention modalities.**