Part I

Obstructive airway disease

1

Asthma

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Introduction

Asthma is a chronic complex inflammatory disorder of the airways characterized by increased airway hyper-reactivity (AHR) and variable airflow obstruction. Its importance is underpinned by the recognition that an estimated 300 million people worldwide suffer from asthma and an estimated additional 100 million persons may be expected to develop the disease by 2025.

Given the magnitude of the potential impact of asthma, one of the key challenges for clinicians and scientists is the possibility of identifying the individuals at highest risk of developing the disease and then intervening in such a manner as to prevent its emergence. This area continues to attract significant interest and more papers have been published this year, with particular interest in intervention with corticosteroids. Once asthma has developed, management involves a number of different healthcare professionals working together with the patient. Lifestyle factors are invariably important, although many patients require pharmacological intervention. Inhaled corticosteroids (ICS) are the most effective anti-inflammatory therapy and are recommended for most patients with symptomatic, persistent disease. Their pre-eminent position is underpinned by clinical studies reporting prompt and effective reductions in asthma symptom scores, improvements in lung function, attenuation of AHR, a reduced incidence of hospitalization and the prevention of death. Nevertheless, important questions have remained unanswered. This year investigators have explored whether in mild asthma it is important to administer inhaled steroids as regular therapy or whether intermittent dosing guided by symptoms is sufficient. We have also seen more information on the relationship between dose and response, and there is some further information on new inhaled steroids.

For those patients whose disease remains inadequately controlled by the use of ICS alone, the addition of long-acting β_2-agonists (LABAs) has been consistently demonstrated to provide additional control, particularly with regard to important end-points such as exacerbations of asthma. This year, further information becomes available as to which dosing level we should choose for add-on therapy with a LABA. The important question of whether the combination of ICS and LABA has any additional anti-inflammatory effect is explored further, and more

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information has become available on the often neglected area of stepping-down therapy. An interesting study has also been published exploring the strategy of using combination inhalers for both maintenance and relief. Leukotriene receptor antagonists remain the second choice for add-on therapy but appear to be beneficial in certain patients. This year we have more information regarding the responsiveness of patients to leukotriene receptor antagonists. Further data are also available on the efficacy of omalizumab in patients with severe asthma, and the novel technique of bronchial thermoplasty, which uses radiofrequency energy to reduce the mass of airway smooth muscle, has been explored in a small number of patients.

Most guideline statements encourage practitioners to develop education and self-management programmes. These programmes have developed with the aim of increasing patients' knowledge and supplying and reinforcing the skill base necessary for the patient (or their carers) to govern changes in their own therapy, the premise being that knowledge leads to improved day-to-day self-management behaviour. However, it remains unclear whether programmes such as these have a role in patients with more severe asthma who have a history of near-fatal attacks.

Preventing the emergence of asthma

The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age

Chan-Yeung M, Ferguson A, Watson W, *et al. J Allergy Clin Immunol* 2005; **116**: 49–55

BACKGROUND. The Canadian Childhood Asthma Primary Prevention Study is a prospective, randomized, controlled trial designed to determine the effectiveness of a multifaceted intervention programme in the primary prevention of asthma in high-risk infants, implemented before birth and in the first year of life.

INTERPRETATION. A multifaceted intervention designed to reduce exposure to allergens and environmental tobacco smoke and to encourage breastfeeding reduced the prevalence of paediatric allergist-diagnosed asthma in children aged 7.

Comment

The authors of this study identified high-risk infants (those with at least one first-degree relative with asthma or two first-degree relatives with other classic immunoglobulin (Ig) E-mediated allergic diseases) and randomly assigned them either to a control group who received the usual care recommended by their primary care physicians, or an active group who received a multifaceted intervention to minimize exposure to house dust mite (encasement of the infant's and parents' bedding, instructions to wash bedding weekly and chemical treatments of carpets and upholstered furniture), exposure to pets (parents were instructed to

remove cats and dogs from the home, or, if this was not possible, to keep any pets outside the home or away from the infant's bedroom) and counselling on smoking cessation and smoke-free homes. Day care was discouraged until after the first year of life and mothers were advised to breastfeed for at least 4 months of the first year. When breastfeeding was not possible, partially hydrolysed whey formula was supplied for supplementation until 12 months of age. Assessment at age 7 included a nurse-led questionnaire on symptoms, examination by a paediatric allergist, determination of AHR by methacholine challenge and allergy skin tests.

The main finding of this study was that the proportion of children recognized by a physician to suffer from asthma was significantly lower in the intervention group (14.9%) than in the control group (23.0%; adjusted risk ratio [RR] 0.44; 95% confidence interval [CI] 0.25–0.79). Interestingly, however, the two groups did not differ with regard to two other atopic diseases: allergic rhinitis and atopic dermatitis. The prevalence and relative risks of reported symptoms in the last 12 months were lower in the intervention group compared with the control group; however, in the same group the prevalence of emergency room visits for wheeze or asthma was higher, and (with regard to the mechanism) it was interesting that there was no effect on the prevalence of AHR or sensitization to common allergens in the intervention group. Looking at a subgroup of patients defined by the presence of AHR and reported wheeze in the last 12 months (derived from a questionnaire interview conducted independently by research nurses) the prevalence of asthma in the intervention group was significantly reduced, by 61%.

The dissociation between reduction in diagnosed asthma and the prevalence of AHR is potentially confusing. Excluding explanation by incorrect diagnoses or bias, the authors argued that AHR (and atopy) may be separate but related factors that contribute to the clinical manifestation of airway disease, and they hypothesized that, for example, if their intervention had reduced the degree of airway inflammation, this may have affected the likelihood that AHR would translate into clinical symptoms. Further assessments are planned when these children reach 11–12 years.

Long-term inhaled corticosteroids in preschool children at high risk for asthma

Guilbert TW, Morgan WJ, Zeiger RS, *et al*. *New Engl J Med* 2006; **354**: 1985–97

BACKGROUND. Focusing therapy in subjects at high risk of developing asthma is an attractive goal as it represents a window of opportunity to either abrogate or modify the disease. Therefore, the authors designed the Prevention of Early Asthma in Kids (PEAK) study to test whether regular treatment with ICS would prevent the development of asthma in pre-school children. The primary outcome measure was the number of episode-free days during the third treatment-free observation year.

INTERPRETATION. The use of regular ICS for 2 years in pre-school children at high risk of developing asthma did not prevent the development of asthma symptoms or affect lung function during a third, treatment-free year.

Comment

The PEAK study randomly assigned 285 subjects at high risk of developing persistent asthma during their pre-school years (identified by an asthma predictive index) to either inhaled fluticasone propionate (88 μg twice daily) or placebo for 2 years. During the third year of the study, medication was discontinued and the primary outcome measure was the number of episode-free days during that year. During the treatment period, the authors found that subjects taking inhaled fluticasone reported a greater proportion of episode-free days, a lower rate of exacerbations and a reduced requirement for supplementary medications compared with placebo. However, following discontinuation of regular therapy during the third year there was no important difference between groups with regard to the proportion of episode-free days. Treatment with ICS was associated with reduced growth during the treatment year but there was evidence of catch-up during the treatment-free year.

Intermittent inhaled corticosteroids in infants with episodic wheezing

Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. *New Engl J Med* 2006; **354**: 1998–2005

BACKGROUND. In order to test whether early intervention with ICS would affect the development of asthma in children with recurrent wheezing episodes, the authors designed the Prevention of Asthma in Childhood (PAC) study as a double-blind, randomized, controlled trial to investigate the effects of intermittent ICS therapy in a cohort of infants whose mothers had received a diagnosis of asthma. They monitored the progression of asthmatic symptoms from birth through the first 3 years of life and used symptom-free days as the primary outcome measure.

INTERPRETATION. Intermittent ICS therapy had no effect on the progression from episodic to persistent wheezing and no short-term benefit during episodes of wheezing in the first 3 years of life.

Comment

Prior observations suggest that the antecedent of impaired lung function in later childhood and adult life observed in patients with persistent wheezing and asthma is an uncontrolled airway inflammatory reaction. Thus, the authors argue that early intervention with anti-inflammatory therapy could affect the natural history favourably. The authors drew their population from a prospective, longitudinal, birth-cohort study: the Copenhagen Prospective Study on Asthma in Childhood

(COPSAC). Infants were recruited following the report of a 3-day episode of wheezing and randomized to either 400 μg/day budesonide or placebo, which was commenced after 3 days of symptoms. As with the study of the use of inhaled fluticasone propionate in wheezy infants discussed below, the results of the study were largely negative. The proportion of symptom-free days did not differ between the two groups and there were no differences with regard to persistent wheezing or the duration of acute episodes. Height and bone mineral density were unaffected. Any study on this age group is beset by the difficulties inherent in recognizing asthma; however, although such difficulties will continue to challenge clinicians and investigators alike, it would seem that treatment with ICS would be unlikely to alter the natural history of asthma.

Secondary prevention of asthma by the use of inhaled fluticasone propionate in wheezy infants (IFWIN): double-blind, randomised, controlled study

Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A. *Lancet* 2006; **368**: 754–62

BACKGROUND. The aim of this study was to investigate whether the introduction of ICS at the earliest identifiable point in the natural history of asthma could prevent subsequent loss of lung function and worsening of asthma in later childhood.

INTERPRETATION. The introduction of early inhaled anti-inflammatory therapy has no effect on the natural history of asthma or wheeze in later childhood and does not prevent loss of lung function.

Comment

This study shared a similar hypothesis and aims to the PAC study (see above). They tested this hypothesis by designing a randomized, double-blind, controlled study of inhaled fluticasone propionate 100 μg twice daily in young children. They identified their participants from a high-risk birth cohort consisting of children having one atopic parent and children who had had an episode of wheeze confirmed by the family doctor. Children were enrolled in the study if they had either two episodes of confirmed wheeze lasting more than 24 h or one prolonged physician-confirmed wheezy episode lasting more than 1 month. The dose of the study drug was reduced every 3 months until the minimum treatment dose was obtained, but if wheeze persisted at 3 months open-label fluticasone propionate 100 μg twice daily was commenced in addition to the study drug. The children were then followed up until the age of 5 years, when the parent or guardian was asked to complete a standard interviewer-administered respiratory questionnaire and specific airway resistance was measured.

Two-thirds of the children were younger than 2 years, most were followed up for more than 3 years and dropouts were few. However, as with previous studies, the

outcome was negative. The authors reported no difference in the proportions of children with current wheeze, physician-diagnosed asthma or use of asthma medication, declining lung function or AHR between those on active treatment and those receiving placebo.

Treatment options for asthma

Inhaled corticosteroids

Daily versus as-needed corticosteroids for mild persistent asthma

Boushey HA, Sorkness CA, King TS, *et al*. *N Engl J Med* 2005; **352**: 1519–28

BACKGROUND. Prompted by observations that patients with asthma infrequently renew prescriptions for controller medications, the authors asked whether this may reflect over-treatment and whether intermittent therapy may therefore be an acceptable strategy in patients with mild persistent asthma. They enrolled 225 patients with mild persistent asthma in a randomized, double-blind, parallel-group trial to investigate the efficacy of short-course corticosteroid treatment guided by a symptom-based action plan alone or in addition to daily treatment with either inhaled budesonide or oral zafirlukast over a 1-year treatment period. The primary outcome measure was morning peak expiratory flow (PEF). Other outcome measures included the pre- and post-bronchodilator forced expiratory volume in 1 (FEV_1), frequency of exacerbations, second degree of asthma control, number of symptom-free days and quality of life.

INTERPRETATION. Further studies are required to determine whether this approach can be recommended.

Comment

The premise of this study was based on the observation that in real life many patients do not adhere to therapy as prescribed and adopt an as-required approach to the management of their asthma. The authors suggest that this may be because many patients do not perceive the need for daily therapy and adopt their own symptom-based action plan. The aim of this study was to determine whether, when following a symptom-based action plan, intermittent corticosteroid therapy would perform as well as either regular inhaled budesonide or oral zafirlukast. Patients were aged 18–65 and were included in the study if they fulfilled the criteria for mild persistent asthma over a 4-week run-in period. Once entered, participants were assigned to one of three parallel treatment groups, which comprised intermittent therapy with either a symptom-based action plan alone, regular inhaled budesonide or regular oral zafirlukast.

With regard to the primary outcome measure, PEF, there was no significant difference among the three groups. As might be expected in patients with mild

asthma, the absolute number of exacerbations was low; however, there was no significant difference between the groups with regard to the number of patients who had one or more exacerbations. Embedded within the study is a recurring message that regular therapy with ICS is associated with important benefits. The authors reported that regular treatment with budesonide was accompanied by significantly greater improvements in the asthma control score, improved lung function (as measured by the pre-bronchodilator FEV_1), AHR, sputum eosinophilia and exhaled nitric oxide. Compared with the intermittent treatment, treatment with zafirlukast did not produce a significantly greater improvement in any outcome. The authors are careful in the interpretation of their results, suggesting that their findings must be considered preliminary and indicating only that symptom-driven intermittent treatment may be possible. Longer and larger studies will be needed before an intermittent approach to prescribing ICS can be recommended.

Once-daily ciclesonide improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma

Pearlman DS, Berger WE, Kerwin E, LaForce C, Kundu S, Banjerji D. *J Allergy Clin Immunol* 2005; **116**: 1206–12

BACKGROUND. The authors designed this study to assess the efficacy and safety of ciclesonide administered once daily in the morning in patients with mild to moderate asthma.

INTERPRETATION. Ciclesonide 80–320 μg once daily in the morning improved lung function and symptoms in patients with mild to moderate persistent asthma. Treatment was well tolerated, with a low incidence of local side effects and no significant effect on the hypothalamic–pituitary–adrenal axis.

Comment

Ciclesonide is a prodrug that, after inhalation, undergoes metabolism by endogenous lung esterases to its active metabolite, desisobutyryl-ciclesonide (des-CIC). The molecule displays high receptor affinity and forms reversible conjugates with lipids in the lung (a possible explanation for the extended residency time within the lung). Systemic bioavailability is typically less than 1%, suggesting that the side-effect profile should be favourable.

In this study the authors analysed data from two identical 12-week multicentre, randomized, double-blind, placebo-controlled, parallel-group studies that included just over 1000 adult patients with mild to moderate asthma. Patients were administered ciclesonide once daily in the morning at one of three doses: 80, 160 and 320 μg. Outcome measures included lung function, asthma symptom scores and safety assessments. All ciclesonide groups showed a modest but significant

improvement in FEV_1 from baseline to week 12 compared with the placebo group (80 μg, 0.12 l; 160 μg, 0.13 l; 320 μg, 0.14 l). Patients taking ciclesonide also showed improvements in FEV_1 percentage predicted, morning and evening PEF, 24-h asthma symptom scores, daily rescue medication use, and night-time awakenings when compared with placebo. The drug was well tolerated and the incidence of oropharyngeal adverse events was no different from placebo. Consistent with the low oral bioavailability, the authors did not find any significant suppression of hypothalamic–pituitary–adrenal axis function (by 24-h urinary cortisol or peak serum cortisol level following cosyntropin stimulation) with any dose of ciclesonide.

Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma

Tomlinson JEM, McMahon AD, Chauduri R, Thompson JM, Wood SF, Thomson NC. *Thorax* 2005; **60**: 282–7

BACKGROUND. Inhaled corticosteroids are the most efficacious anti-inflammatory therapy for patients with persistent asthma; however, most clinical trials exclude cigarette smokers. This group from Glasgow, UK, had previously shown that the efficacy of ICS is reduced in current cigarette smokers. Exploring this further, the authors designed a randomized, double-blind, parallel-group study comparing the efficacy of 400 or 2000 μg of inhaled beclomethasone daily in smokers and non-smokers.

INTERPRETATION. Smokers with mild persistent asthma show a relative corticosteroid resistance that can be overcome by using higher doses.

Comment

The authors recruited 95 patients with persistent asthma from both primary and secondary care clinics in Glasgow. The primary end-point was the change in morning PEF. After 12 weeks of treatment the authors were able to show that the morning PEF improved in the non-smoking group but showed no improvement in the smoking group. In patients receiving 400 μg daily of inhaled beclomethasone there was a large difference in the morning PEF (mean difference –25; 95% CI –45 to –4; adjusted $P = 0.019$) and smokers reported more exacerbations of asthma than non-smokers (6 vs 1). In non-smoking patients receiving 2000 μg daily of inhaled beclomethasone an improvement in morning PEF was seen, as expected; however, smoking patients also showed a small improvement in PEF, and there was no difference in exacerbation rates between the two groups, suggesting that the insensitivity to corticosteroids could be overcome by using larger doses. No

differences in compliance were found between non-smokers and smokers.

Monitoring exhaled nitric oxide to guide inhaled steroid dosage in asthma

Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. *N Engl J Med* 2005; **352**: 263–73

BACKGROUND. Current guideline statements recommend that the dose of ICS should be titrated according to asthma control, as judged by reported symptoms and lung function. The authors of this study designed a prospective, randomized, single-blind, placebo-controlled trial to test whether the use of an algorithm based on the fraction of exhaled nitric oxide (FE_{NO}) had the potential to guide dose adjustment of ICS therapy and improve asthma control.

INTERPRETATION. Measurements of FE_{NO} may be used to facilitate dose adjustments of ICS in adult patients with chronic persistent asthma.

Comment

The authors recruited 110 patients (mean age 44.8 years, 63% women) from primary care who had chronic asthma and were receiving regular ICS. During the first phase of the study a considerable amount of effort was put into optimizing the dose of fluticasone (the ICS chosen for the study) so that patients commenced the second phase of the study from a stable baseline. After this first phase, subjects were randomly assigned to one of two management groups: a control group and a nitric oxide group. In the control group treatment decisions were made in response to reported symptoms, bronchodilator use and lung function (according to current Global Initiative for Asthma [GINA] guidelines) and in the nitric oxide group treatment decisions were based solely on FE_{NO}.

The main finding from the study was that participants in the FE_{NO} arm ended up requiring a lower maintenance dose of ICS (370 μg fluticasone/day) than those whose treatment decisions were based on symptoms, bronchodilator use and lung function (641 μg fluticasone/day) without any important difference in other markers of control, including the cumulative total number of exacerbations, time to first exacerbation, or the numbers of patients with one or more exacerbations. Although the authors observed a reduction of just over 45% in the number of exacerbations per patient per year, this was not deemed clinically significant. It is also noteworthy that no significant differences were observed with regard to a range of symptoms or the magnitude of airway inflammation, as measured by the percentage of eosinophils in induced sputum.

One significant problem with the study is that, rather than concentrating on increasing doses of inhaled fluticasone, current guidelines suggest that most clinicians would opt to introduce a LABA rather than increase ICS when asthma control is suboptimal; however, this would have required a much larger study and may have confounded the primary end-point. It may also be recognized that

designing a study in which three parameters may effect a treatment change in one arm but only one parameter does so in the other arm will favour more treatment changes to be made in the arm of the study with the greater number of parameters.

Titrating steroids in exhaled nitric oxide in children with asthma: a randomized controlled trial

Pijnenburg MW, Bakker EM, Hop WC, De Jongste J. *Am J Respir Crit Care Med* 2005; **172**: 831–6

BACKGROUND. The authors of this study explore a similar idea to that of Smith and colleagues (see above), investigating the utility of adjusting the dose of ICS on the basis of exhaled nitric oxide measurements in children. They postulated that titration of the ICS dose with reference to both FE_{NO} and symptoms would result in the administration of lower doses of inhaled steroid and better asthma control compared with titration of the steroid dose according to symptom scores alone.

INTERPRETATION. The use of FE_{NO} to guide the dose of ICS in children with allergic asthma achieves reduction in AHR without increasing the dose of steroids compared with treatment adjustments based on symptoms alone.

Comment

This study shares a similar premise to that conducted by Smith and colleagues but focuses on children with atopic asthma. Pijnenburg and colleagues studied 85 children aged between 6 and 18 years with atopic asthma and randomly allocated them to one of two groups stratified for baseline FE_{NO} ($\geq$30 or <30 p.p.b.) and dose of ICS ($\geq$400 or <400 μg budesonide or equivalent daily dose). The study ran over 12 months and patients were assessed at 3-monthly intervals. In one group (FE_{NO} group), ICS doses were adjusted in accordance with an agreed algorithm based on both the FE_{NO} and symptoms, and in the other group (symptom group) dose adjustments were based on symptoms alone. Although the authors had speculated that incorporating FE_{NO} would result in the administration of lower doses of ICS, this did not prove to be the case: in both groups there was no significant difference between the dose of steroids used; however, the degree of AHR improved significantly more in the FE_{NO} group than in the symptom group (2.5 vs 1.1 doubling doses; $P = 0.04$). As AHR is a major determinant of asthma prognosis and is associated with reduced growth of airway calibre in childhood and an accelerated decline of lung function in adulthood, the authors speculated that the FE_{NO} strategy may have the potential to improve the long-term outcome of childhood asthma. Clearly, this would need to be endorsed by adequately designed studies. Although there was no difference in FE_{NO} between the two groups at the start of the study, the FE_{NO} increased in the symptom group (32% higher): in the symptom group there was a significant increase in FE_{NO}, from 30.8 to 36.7 p.p.b.

($P = 0.035$).

Inhaled corticosteroids and long-acting β_2-agonists

Moderate dose inhaled corticosteroid plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma

Masoli M, Weatherall M, Holt S, Beasley R. *Thorax* 2005; **60**: 730–4.

BACKGROUND. The recently published British Thoracic Society guidelines endorse the addition of a LABA drug as first-line add-on therapy at step 3 in patients not controlled on ICS alone. However, such advice is based on studies including dose ranges from 200 to 800 μg/day of beclomethasone dipropionate or equivalent. It remains unclear at what dose of ICS within this range clinicians should consider introducing concomitant LABA treatment. The authors of this study compared the clinical benefit of adding salmeterol in patients not controlled on moderate doses of ICS (200 μg/day fluticasone or equivalent) with increasing the dose of ICS at least twofold.

INTERPRETATION. In patients symptomatic on ICS at a dose of 200 μg fluticasone or equivalent, the addition of salmeterol is superior to increasing the dose of ICS at least twofold for all major clinical outcome measures. The results of this meta-analysis suggest that salmeterol should be considered when asthmatics remain symptomatic despite moderate doses of ICS such as fluticasone 200 μg/day or equivalent.

Comment

When asthma remains poorly controlled on ICS therapy, the British Thoracic Society guidelines recommend the addition of a LABA as the first choice. However, this advice encompasses a fourfold dose range of ICS (200–800 μg/day beclomethasone dipropionate or equivalent). Recent information on dose– response curves though suggests that the maximum effect of ICS is achieved at much lower doses than previously thought. In an attempt to compare the benefits of the two medications, the authors of this study compared the clinical benefit of adding salmeterol in patients not controlled on moderate doses of ICS (200 μg/day fluticasone or equivalent) with the benefit of increasing the dose of ICS at least twofold. Data were obtained from twelve studies with just over 4500 subjects with moderate to severe asthma. The primary outcome measures were the number of subjects withdrawn because of asthma and the number of subjects with at least one moderate or severe exacerbation. Secondary outcome measures included morning and evening PEF, FEV_1, night awakenings, and daytime and nighttime α_2-agonist use.

With regard to the primary outcomes of the study, the authors reported that there was a significant reduction in the number of subjects withdrawn because of

asthma in the low-dose ICS/salmeterol group (59/2036) compared with the high-dose ICS treatment (86/1992) (odds ratio [OR] 1.58; 95% CI 1.12–2.24). More subjects in the low-dose ICS/salmeterol group reported one or more moderate or severe exacerbations of asthma (184/2312) compared with high-dose ICS treatment (243/2264): OR 1.35 (95% CI 1.10–1.66). Secondary outcomes were also better in the ICS/salmeterol group.

Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study

Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. *Lancet* 2006; **368**: 744–53

BACKGROUND. Turning again to the question of the dose of ICS at which a LABA should be initiated, the authors of this study designed a double-blind, parallel-group study to assess whether patients with moderate to severe persistent asthma who remained symptomatic despite regular budesonide/formoterol combination maintenance therapy would benefit from additional budesonide/formoterol administered as reliever therapy.

INTERPRETATION. In patients with moderate to severe asthma who remain symptomatic despite regular combination therapy with budesonide/formoterol, the use of as-needed budesonide/formoterol reduces the risk of severe exacerbations compared with as-needed formoterol or as-needed terbutaline.

Comment

The rapid onset of action of formoterol provides a rationale for its use as a reliever as well as a controller medication and its use as such has been shown to reduce the number of asthma exacerbations compared with terbutaline in symptomatic patients despite regular budesonide treatment. In order to determine whether patients using formoterol/budesonide combination would also benefit, the authors enrolled around 3400 patients from 289 centres in 20 countries. To be eligible for entry, patients had to have symptomatic moderate to severe persistent asthma despite the regular use of combination therapy. Enrolled patients were assigned to one of three alternative reliever strategies: budesonide/formoterol, formoterol or terbutaline.

The main finding was that the time to first severe exacerbation (the primary outcome measure in this study, which was defined as an event resulting in hospitalization, emergency room treatment or both, or the need for oral steroids for $\geq$3 days) was significantly longer in patients using as-needed budesonide/formoterol versus formoterol ($P = 0.0048$, log-rank test) and with as-needed formoterol versus terbutaline ($P = 0.0051$). The rate of severe exacerbations was also reduced when taking as-needed combination therapy compared with

formoterol. The authors reported a greater number of asthma control days in all treatment groups and all treatments were well tolerated.

This is an interesting study raising the potential for a new paradigm in asthma management. Concerns that such a strategy would result in patients administering excessive amounts of ICS were not realized. However, as alluded to in the accompanying editorial by Professor Pedersen from Denmark, a study should be designed comparing this strategy to an increase in the daily dose of combination therapy.

Adding salmeterol to an inhaled corticosteroid: long term effects on bronchial inflammation in asthma

Koopmans JG, Lutter R, Jansen HM, van der Zee JS. *Thorax* 2006; **61**: 306–12

BACKGROUND. Although the addition of a LABA to an ICS consistently improves clinical outcomes, it is not known whether there is any additional anti-inflammatory effect. The authors of this study designed a randomized controlled trial to run over 1 year in which the primary outcomes included sputum eosinophil and eosinophilic cationic protein concentration and secondary outcomes included neutrophil-associated sputum parameters and a marker of respiratory membrane permeability.

INTERPRETATION. The authors did not observe any sustained anti-inflammatory effect; however, they noted an improvement in the size selectivity of plasma protein permeation across the respiratory membrane.

Comment

Clinical studies have consistently demonstrated that the addition of a LABA to an ICS results in consistent improvements in a range of clinical outcomes, including symptom control and the exacerbation rate. However, to date no convincing effect has been shown on the underlying inflammatory asthmatic process. In this study the authors enrolled 54 patients with mild to moderate persistent allergic asthma, who were randomized to receive either fluticasone 250 μg twice daily or fluticasone/salmeterol 250/50 μg twice daily. Compared with subjects receiving fluticasone alone, those randomized to fluticasone/salmeterol demonstrated improved lung function, improved symptom scores, a reduced requirement for rescue medication and improved bronchial hyper-reactivity; however, using induced sputum to assess a range of eosinophil and neutrophil markers of inflammation, they were unable to demonstrate any convincing sustained anti-inflammatory effect. The one positive finding was that subjects receiving the combination therapy displayed a significantly reduced ratio of α_2-macroglobulin to albumin compared with those

receiving fluticasone alone. This may suggest that the permeability of the respiratory membrane is improved by the addition of salmeterol.

Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down

Bateman E, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. *J Allergy Clin Immunol* 2006; **117**: 563–70

BACKGROUND. Current international asthma guidelines recommend that once asthma control has been achieved and maintained for 3–6 months, treatment should be reviewed and dose reduction of controller medication should be attempted, with careful monitoring to ensure that control is not lost. This advice is largely based on clinical experience, and few studies have examined the options and most favourable conditions for stepping down treatment. The authors of this paper designed a prospective, double-blind, controlled study in which, using a very similar definition of asthma control to that used in the Gaining Optimal Asthma ControL (GOAL) study, they compared the effects on features of asthma of reducing either the inhaled LABA or the ICS component once control had been attained with fluticasone propionate/salmeterol in previously steroid-naive patients with chronic asthma.

INTERPRETATION. Treatment with a lower dose of ICS and a LABA is a more effective treatment option than treatment with a higher dose of ICS alone.

Comment

In order to assess two options for stepping down asthma therapy, the authors selected patients who achieved well-controlled status on fluticasone propionate/salmeterol 250/50 μg twice daily after 12 weeks of treatment. These patients were then randomized to either fluticasone propionate/salmeterol 100/50 μg twice daily or fluticasone propionate 250 μg twice daily. As might be expected, improvements in baseline lung function were obtained during the 12-week open-label part of the study; however, during the double-blind treatment period the mean morning PEF was maintained only in the group receiving fluticasone propionate/salmeterol 100/50 μg twice daily. In contrast, mean morning PEF decreased in patients treated with fluticasone propionate 250 μg twice daily. For each week of the double-blind treatment period, the proportion of patients with asthma assessed as well controlled or totally controlled was slightly lower than that seen during the last week of open-label treatment but the proportion controlled each week with fluticasone propionate/salmeterol 100/50 μg remained higher than with fluticasone

propionate 250 μg.

Inhaled corticosteroids and leukotriene receptor antagonists

Characterization of within-subject responses to fluticasone and montelukast in childhood asthma

Szefler SJ, Phillips BR, Martinez FD, *et al*. *J Allergy Clin Immunol* 2005; **115**: 233–42

BACKGROUND. The recognition that a considerable amount of interindividual variability exists in the response to ICS and the response to leukotriene receptor antagonists suggests that more information is needed to allow the clinician to tailor therapy for individual patients. This study, conducted under the auspices of the Childhood Asthma Research and Education Network of the National Heart, Lung and Blood Institute, was designed to examine the variability of response to ICS and leukotriene receptor antagonists in children with the aim of identifying indicators that would allow prediction of a successful response to either medication.

INTERPRETATION. Significantly more children show a clinically meaningful FEV_1 response to an ICS than a leukotriene receptor antagonist.

Comment

The authors recruited 144 children with mild to moderate asthma aged between 6 and 17 years, and randomized them to one of two crossover sequences, including 8 weeks of fluticasone propionate (100 μg twice daily) and 8 weeks of the leukotriene receptor antagonist montelukast (using either a 5 or 10 mg dose depending on the age of the child). The trial ran over 18 weeks and 126 children (out of 144) completed the study. Defining response as an improvement in FEV_1 of 7.5% or greater, 17% of the 126 participants responded to both medications, 23% responded to fluticasone alone and 5% to montelukast alone. Interestingly, 55% did not respond to either medication. A favourable response to fluticasone appeared to be predicted by the presence of higher levels of exhaled nitric oxide, total eosinophil count, serum IgE, serum eosinophilic cationic protein and lower levels of AHR and lung function. A favourable response to montelukast appeared to be associated with a younger age and shorter disease duration. A greater differential response to fluticasone over montelukast was associated with greater bronchodilator response, exhaled nitric oxide level and eosinophilic cationic protein level, and a lower methacholine PC_{20} (20% fall in FEV, in response to methacholine challenge) and pulmonary function values. The 55% of patients who failed to demonstrate a

significant response to either agent despite reporting symptoms tended to have better lung function and less evidence of allergic inflammation.

Response profiles of fluticasone and montelukast in mild-to-moderate persistent childhood asthma

Zeiger RS, Szefler SJ, Phillips BR, *et al. J Allergy Clin Immunol* 2005; **117**: 45–52

BACKGROUND. Recognizing the need for evidence on outcome from the use of either ICS and leukotriene receptor antagonists in children, the authors interrogated data from a multicentre, double-masked, two-sequence, 16-week crossover trial in order to determine intraindividual and interindividual response profiles and predictors of response.

INTERPRETATION. Inhaled corticosteroids have a superior clinical, pulmonary and anti-inflammatory profile in children with mild to moderate asthma compared with leukotriene receptor antagonists.

Comment

Inhaled corticosteroids should be preferred to leukotriene receptor antagonists in adults with asthma; however, fewer data are available to make a similar definitive statement in children. In this study the authors drew on a clinical trial being coordinated by The National Heart, Lung, and Blood Institute Childhood Asthma Research and Education Network in children with mild to moderate persistent asthma. One hundred and twenty-seven (out of 144) children aged between 6 and 17 years completed a randomized trial in which they were assigned to one of two crossover treatment periods (separated by a 4-week washout period) involving 8 weeks on either inhaled fluticasone propionate 100 μg twice daily or montelukast (a daily dose of 5 or 10 mg depending on the age of the child).

Consistent with the known efficacies of the two agents, the investigators reported improvements in most clinical outcomes in both limbs of the study; however, fluticasone was significantly better than montelukast with regard to the number of asthma control days, the asthma control questionnaire score, use of reliever medication, lung function and exhaled nitric oxide. They also noted that exhaled nitric oxide provided an indication of the likely number of asthma control

days and could prove a useful predictor of the response to ICS.

Omalizumab

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

Humbert M, Beasley R, Ayres J, *et al*. *Allergy* 2005; **60**: 309–16

BACKGROUND. A subgroup analysis of previous studies using omalizumab had suggested that this drug would prove beneficial to patients with severe persistent asthma. Here the authors conducted a randomized, placebo-controlled, double-blind study over a 28-week period to establish the efficacy, safety and tolerability of omalizumab in patients whose asthma remained poorly controlled despite GINA step 4 interventions, including high-dose ICS plus LABA and additional controller medication if required.

INTERPRETATION. Omalizumab significantly reduced exacerbation rates in patients with asthma whose disease remained uncontrolled despite GINA step 4 interventions. Benefits were also seen with regard to quality of life, symptom control and lung function.

Comment

Patients with severe persistent asthma are fortunately a minority but constitute an important subgroup of patients who continue to experience symptoms and frequent exacerbations. They make a significant contribution to asthma-related health expenditure; indeed, more than half the patients enrolled by Humbert *et al.* had required emergency room assessment in the year before the study, more than one-third had required admission to hospital and 10% had been admitted to an intensive care unit.

In this study the authors enrolled 482 patients with severe persistent asthma (requiring regular treatment with >1000 μg/day beclomethasone dipropionate or equivalent and LABA [GINA step 4]) with reduced lung function (mean FEV_1 = 61% predicted) and an allergic phenotype (positive skin prick test to at least one perennial aeroallergen to which they were likely to be exposed during the study, and a total IgE level of ≥30 to ≤700 IU/ml). They also had to have reported at least two exacerbations requiring systemic corticosteroids or one severe exacerbation in the past 12 months. The primary efficacy variable was the rate of clinically significant asthma exacerbation (defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids) during the 28-week treatment phase. The primary intention-to-treat (PITT) population (a total of 419 patients) was, on advice from the European Union Committee on Proprietary Medicinal Compounds (CPMP), deemed to be the patient population randomized after

implementation of the protocol amendment (CPMP) and reflected the updated GINA guidelines.

After adjustment (PITT population), the clinically significant asthma exacerbation rate was 26% lower in patients receiving omalizumab than in those receiving placebo (0.68 compared with 0.91); this difference was statistically significant. The number needed to treat for 1 year to save one clinically significant exacerbation was 2.2. Omalizumab halved the rates of severe asthma exacerbations (0.24 vs 0.48; $P = 0.002$) and emergency visits (0.24 vs 0.43; $P = 0.038$), and the number needed to treat to save one severe exacerbation was also 2.2. Omalizumab also significantly improved asthma-related quality of life, morning PEF and asthma symptom scores. The study also provided reassuring safety data in that the incidence of adverse events was similar between treatment groups and the total incidence of injection site reactions was 5.3% with omalizumab. This study provides evidence that omalizumab may be a useful add-on therapy in patients whose asthma remains poorly controlled despite GINA step 4 strategies.

Smoking cessation

Effects of smoking cessation on lung function and airway inflammation in smokers with asthma

Chaudhuri R, Livingston E, McMahon AD, *et al. Am J Respir Crit Care Med* 2006; **174**: 127–33

BACKGROUND. Around one-fifth of patients with asthma smoke and probably as a consequence of this experience more symptoms, are more likely to present to hospital, experience an accelerated decline in lung function, and have relative corticosteroid resistance. To date, there has been very little published work exploring the effects of stopping smoking in patients with asthma. The authors of this study examined the short-term effects of smoking cessation on lung function, airway inflammation and corticosteroid responsiveness in patients with asthma who smoke.

INTERPRETATION. Smoking cessation is followed by a rapid and considerable improvement in lung function and a fall in sputum neutrophil counts.

Comment

This study is from the same group in Glasgow, UK, whose paper is discussed earlier in this chapter (Tomlinson *et al.*, 2005) In this prospective controlled study, the team enrolled 32 smoking asthmatics who were willing to consider stopping. They underwent a baseline assessment that included measurement of lung function, measurement of inflammatory cells in induced sputum, assessment of the cutaneous vasoconstrictor response to topical beclomethasone, airway responsiveness to oral prednisolone, and a peripheral blood lymphocyte proliferation assay. Assessments were repeated 1, 3 and 6 weeks into the study.

They recruited 32 subjects, of whom 11 wished to continue smoking and 21 decided to attempt smoking cessation. Smoking cessation is challenging, and the authors found that by the end of 1 week seven had relapsed and by the end of the study a further four had started smoking again. However, for those who managed to stop smoking the benefits in terms of lung function were rapid and impressive. The mean (SD) change in FEV_1 in those quitting was 356 (278) ml at the end of week 1, 390 (311) ml at the end of week 3 and 450 (471) ml at the end of week 6. There was no change in the equivalent FEV_1 measures in the smoking control group. At week 6, compared with the smoking controls, the mean improvement in FEV_1 in those who stopped smoking was 407 ml, which represented 15.2% in FEV_1 predicted. The improvement in PEF was 93 l/min.

Consistent with other studies, the authors found that smokers had a raised sputum neutrophil count, and although the authors were able to demonstrate that the neutrophil levels declined after smoking cessation, there were no changes in the levels of sputum supernatant mediators. The improvement in FEV_1 did not appear to relate to the changes in neutrophil numbers.

Smoking cessation did not improve corticosteroid responsiveness; however, the authors speculated that this may have been because the baseline lung function improved by such a large amount that there was little room for further improvement. No differences between groups were noted in the cutaneous vasoconstrictor response or lymphocyte proliferation assay.

Pneumococcal vaccination

Asthma as a risk factor for invasive pneumococcal disease

Talbot TR, Hartert TV, Mitchel E, *et al*. *N Engl J Med* 2005; **352**: 2082–90

BACKGROUND. Pneumococcal vaccination is currently recommended for patients with chronic obstructive pulmonary disease but not asthma. The authors of this paper designed a nested case–control study using data from two large populations and then, using Tennessee's Medicaid programme, performed a cohort analysis to estimate the incidence of invasive pneumococcal disease in persons with and without asthma.

INTERPRETATION. The risk of invasive pneumococcal disease in persons with asthma is at least double that in controls, and asthma therefore represents an independent risk factor for this condition.

Comment

Data from this study was drawn from two Tennessee disease registries that form part of the Active Bacterial Core surveillance (ABCs) network for the Centres for Disease Control and Prevention (CDC), providing a study population of nearly 3 million. From this, the authors conducted a nested case–control study enrolling subjects between the ages of 2 and 49 years covered by Tennessee's Medicaid pro-

gramme (TennCare). Over the period of the study the authors identified just over 600 cases of invasive pneumococcal disease (defined as isolation of *Streptococcus pneumoniae* from a normally sterile site) and just over 6000 controls. A diagnosis of asthma was based on assignation of the diagnosis from one emergency department attendance, two outpatient visits, or the prescription of asthma-related medications. High-risk asthma was defined as asthma requiring admission to hospital or an emergency department. Following adjustment for other recognized risk factors, persons with asthma had more than twice the risk of pneumococcal disease (adjusted OR 2.4; 95% CI 1.9–3.1) compared with controls. The observed increased risk remained after adjustment for the use of long-term (<120 days per year) oral corticosteroids. The authors argue that the strength of this finding suggests that persons with asthma should be considered for pneumococcal vaccination.

Peak flow monitoring

A randomized clinical trial of peak flow versus symptom monitoring in older adults with asthma

Buist AS, Vollmer WM, Wilson SR, Frazier A, Hayward AD. *Am J Respir Crit Care Med* 2006; **174**: 1077–87

BACKGROUND. Guideline statements endorse the use of patient education and self-management, including the use of peak flow readings for asthma, particularly in adults with moderate to severe asthma and a history of exacerbations. However, only a minority of patients keep a peak flow meter and an even smaller number use one regularly. In studies endorsing the use of peak flow readings it can be difficult to separate the usefulness of the peak flow readings from that conferred by other aspects of the intervention. The authors of this study designed a randomized, controlled trial to determine whether the use of peak flow readings in addition to symptom monitoring would be superior to symptom monitoring alone as a management tool in older adults with moderate to severe asthma.

INTERPRETATION. When used as part of a comprehensive asthma management programme, peak flow monitoring had no advantage over symptom monitoring in older adults with moderate to severe asthma.

Comment

In this study the authors identified nearly 300 patients aged between 50 and 92 years from a large managed care organization. Participants were randomly assigned to either symptom monitoring or peak flow monitoring interventions. The interventions were delivered through the use of four 90-min small group classes during which a personalized asthma action plan was developed and inhaler technique checked. The primary outcome measures were healthcare utilization and asthma-specific quality of life. The secondary outcome measure was lung function. No significant differences were found between the groups with regard to the primary or

secondary outcome measures. Although it is often suggested that patients do not comply with long-term peak flow monitoring, the authors found that most patients randomized to peak flow monitoring persisted throughout the study, confirming that lapses in this arm did not contribute to the lack of difference between groups.

The Coping with Asthma Study: a randomised controlled trial of a home-based, nurse-led pschoeducational intervention for adults at risk of adverse asthma outcomes

Smith JR, Mildenhall S, Noble MJ, *et al*. *Thorax* 2005: **60**; 1003–11

BACKGROUND. Management strategies in asthma encourage the use of self-management asthma programmes. However, it is unclear at present whether the evidence of effectiveness of these programmes can be extrapolated to patients who present with fatal and near-fatal asthma. The authors designed what they felt was a pragmatic randomized controlled trial to assess effectiveness as it would be as part of normal care in a home-based programme delivered by a respiratory nurse specialist (intervention) compared with usual care (control). By necessity, the study was unblinded since additional liaison with health professionals involved in the care of study patients often formed part of the intervention.

INTERPRETATION. The effectiveness of a home-based, nurse-led psychological intervention is limited in adult asthma patients at risk of adverse outcomes.

Comment

Although self-management asthma programmes are effective in general asthma populations, patients who present with fatal or near-fatal attacks are subject to a complex interplay of clinical and psychosocial factors that are likely to reduce the effectiveness of these programmes. In particular, the recognition that these patients display a high prevalence of psychosocial factors lends support to the proposition that a home-based psychoeducational intervention may influence their presentation; however, it is uncertain whether any such intervention would be more likely to be effective, given the greater capacity for benefit, or less effective, given the impact of the psychosocial barriers to education and behaviour change.

The authors identified patients with severe asthma (British Thoracic Society step 4 or 5) that they felt to be at risk of severe events (history of non-attendance at clinics, lack of adherence to treatment, and clinical judgement) from adult asthma clinics at five hospitals in Norfolk and Suffolk, UK, and ten general practices in Norfolk. Patients were randomized to either a control arm, in which they continued with their routine asthma care as provided by primary and secondary health services, or the intervention arm, in which they received 6 months of home visits (plus supplementary telephone calls) by a specialist nurse delivering a psychoeducational programme.

Unfortunately, the results of the study were largely negative. After 6 months

there were no important or significant differences between the usual care and intervention groups in mean symptom control, physical functioning or mental health scores. Although the authors did report small apparent benefits of the intervention on asthma-specific quality of life for up to 12 months and short-term effects on generic health status, the interpretation of the benefit or magnitude of these was difficult.

Bronchial thermoplasty for asthma

Cox G, Miller JD, McWilliams A, Fitzgerald JM, Lam S. *Am J Respir Crit Care Med* 2006; **173**: 965–9

BACKGROUND. Bronchial thermoplasty delivers energy to the airway wall at radio frequency, which has been shown to reduce the contractility of airway smooth muscle. It therefore has the potential to reduce AHR and improve asthma control. The object of this study was to examine the safety of the technique in patients with mild to moderate asthma and observe the impact on lung function and AHR.

INTERPRETATION. Bronchial thermoplasty is well tolerated and produces sustained improvements in AHR for at least 2 years.

Comment

Bronchial thermoplasty delivers radio frequency energy to the airway in a controlled manner at an intensity sufficient to heat the tissue to around 65°C, which avoids tissue destruction and scarring but reduces the mass of airway smooth muscle. The technique targets the airways distal to the mainstem bronchi down to an airway diameter of 3 mm. In this non-randomized, prospective study the investigators applied the technique to 16 subjects with asthma of mild to moderate severity. The work was performed at two sites; at one site the technique was performed with the patient under general anaesthesia and at the other the patient was under local anaesthesia with conscious sedation. The airways treated were those that were beyond the lobar bronchi but accessible to the bronchoscope, and larger than 3 mm in diameter. The authors reported that typically one treatment session was needed to treat the airways in each lower lobe and a further session to treat the upper lobes. Treatment sessions were at least 3 weeks apart.

A total of 49 bronchoscopic procedures were performed and all treatments were completed in 30 min or less. Apart from transient acute blanching of the airway wall, no sustained changes were reported with regard to the shape size or structure of the airways. Increased cough, dyspnoea, wheeze and bronchospasm represented the most frequently reported adverse events and the majority of side effects were deemed to be mild (130/155). A small number of moderate adverse events were noted (25/155); there were no serious adverse events. An improvement in AHR was observed in all 16 subjects, the mean PC_{20} increasing by 2.37 ± 1.72 (P <0.001), 2.77 ± 1.53 (P <0.007) and 2.64 ± 1.52 doublings (P <0.001) at 12 weeks, 1 year and

2 years after the procedure respectively. Subjects also reported significant improvements over baseline in symptom-free days and both morning and evening peak flow. In terms of long-term safety, the investigators observed no deterioration in spirometry or change in CT scan appearances after 2 years.

As the authors acknowledge, the study was designed to evaluate feasibility and safety, not efficacy; however, the results give confidence to suggest that further studies should proceed.

Acute asthma

Comparison of inhaled fluticasone with intravenous hydrocortisone in the treatment of adult acute asthma

Rodrigo GJ. *Am J Respir Crit Care Med* 2005; **171**: 1231–6

BACKGROUND. The prescription of systemic corticosteroids is endorsed as a key component of the management of acute exacerbations of asthma but ICS are generally considered to be ineffective. However, several studies have suggested there may be some merit in exploring whether this traditional view should continue to be held. The author of this study designed a double-blind randomized trial to investigate the effect of high and repeated doses of fluticasone propionate with standard treatment in adult patients with acute severe asthma.

INTERPRETATION. The sequential delivery of high doses of fluticasone produces therapeutic effects as soon as 90 min after commencing treatment.

Comment

The authors recruited 106 patients presenting to the Emergency Department of the Hospital Central de las Fuerzas Armadas in Montevideo, Uruguay, with acute severe asthma. Fluticasone was administered by metered-dose inhaler (MDI) using a spacer (Volumatic) in a dose of two puffs at 10-min intervals for 3 h, giving a total dose of 3000 μg/h. Patients randomized to the systemic steroid arm received 500 mg of intravenous hydrocortisone at the beginning of treatment. All patients received four puffs of albuterol and ipratropium bromide (2400 μg of albuterol and 504 μg of ipratropium) per hour.

Patients randomized to fluticasone displayed an overall 30.5% (95% CI 6.3–54.7%) greater improvement in PEF than those receiving hydrocortisone. Notably, the improvement in patients receiving fluticasone was rapid, resulting in better peak flows at 120, 150 and 180 min. Fluticasone-treated patients also achieved discharge criteria at a faster rate than those receiving fluticasone. The fluticasone effect appeared to be greater in those with the poorest lung function. The authors speculated that the beneficial effects are probably a non-genomic steroid effect and may be attributed to enhanced noradrenergic neurotransmission

in the airway vasculature promoting vasoconstriction and possibly mucosal decongestion.

The effect of telithromycin in acute exacerbations of asthma

Johnston SL, Blasi F, Black PN, Martin RJ, Farrell DJ, Nieman RB. *New Engl J Med* 2006; **354**: 1589–600

BACKGROUND. The Telithromycin, Chlamydophila, and Asthma Trial (TELICAST) was designed to determine whether a 10-day course of telithromycin improved symptoms and peak flow in patients with an acute exacerbation of asthma compared with placebo. The primary end-point was a change in symptom score and morning PEF.

INTERPRETATION. The authors concluded that telithromycin may be of benefit in patients with acute exacerbations of asthma.

Comment

Ketolides are a new class of antibiotics that are structurally related to macrolides and have a bactericidal effect against *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*; however, in addition they are known to possess immunomodulatory effects. The authors enrolled 278 patients within 24 h of an acute exacerbation of asthma and randomly assigned participants to receive either telithromycin (800 mg daily for 10 days) or placebo in addition to their usual care. As current guidelines do not endorse the prescription of antibiotics as routine for the management of asthma, the authors specifically aimed to recruit patients with no clinically obvious need for an antibiotic and therefore excluded those deemed to have overt infection. They chose two primary end-points: change from baseline over the treatment period in symptoms and the morning PEF at home.

Of the two primary outcome measures, only asthma symptoms showed a significant improvement, the telithromycin group showing a mean decrease in symptom score of 1.3 points compared with 1.0 point in the placebo group (mean difference –0.3 point; 95% CI 0.5 to –0.1; $P = 0.004$), which was equivalent to a 40.4% reduction in symptoms compared with 26.5%. PEF did not differ significantly between the groups.

The presence of *C. pneumoniae* or *M. pneumoniae* was sought by performing serological analysis, polymerase chain reaction and culture. Somewhat surprisingly, around 60% of patients met at least one of the criteria for infection with *C. pneumoniae*, *M. pneumoniae* or both; however, it is unclear from this study whether the mechanism of apparent benefit relates to antibacterial or immunomodulatory activity. The authors allude to the need for further studies and highlight concern that recent reports have emphasized rapidly aggressive hepatotoxicity associated with telithromycin.

Conclusion

The field of asthma research continues to generate important and challenging research. The goal of preventing the emergence of asthma remains tantalizing and elusive. There are hints that multifaceted programmes such as that adopted by the Canadian Childhood Asthma Primary Prevention Study may have some benefit; however, it does appear clear that using ICS is not appropriate. ICS remain the mainstay of prophylactic anti-inflammatory therapy and once again are shown to be more efficacious than leukotriene receptor antagonists; however, although we may accept that many patients may use such therapies on an *ad hoc* basis, strategies recommending this approach cannot be endorsed. Cigarette smoking is a major contributor to relative corticosteroid resistance, alerting clinicians to the need for the prescription of higher doses in smoking asthmatics. Conversely, stopping smoking confers benefits for lung function and airway inflammation. Although asthma is fundamentally an inflammatory disease and ICS are administered for the purposes of controlling inflammation, until recently we have only been able to infer the airway inflammatory response by assessing reported symptoms and lung function. The development of techniques to measure airway inflammation, specifically the fraction of expired nitric oxide, may provide a useful tool to guide decision-making, particularly in children, although it is likely that more studies will be needed, especially in adults, before day-to-day confidence emerges. The LABAs have made an extremely important contribution to the management of asthma and have become established as the most efficacious add-on therapy, although the precise mechanisms remain elusive. However, not only can they allow asthma control to be improved, but they also facilitate step-down therapy without loss of control. The importance of smoking cessation notwithstanding, the development of new therapies for selected patients with asthma remains an important goal. Studies with omalizumab suggest that it has potential in selected atopic asthmatics and this year we have evidence that the drug has potential in patients with the severest spectrum of the disease. The development of bronchial thermoplasty also appears to offer promise to selected patients and future studies will undoubtedly be awaited with interest. Finally, as ever challenging, the development of techniques to help patients accept responsibility for the management of this illness remains an important goal and requires input from a variety of health professionals, including, in certain situations, specialist psychologists.