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REVIEW

The ADMIT series – Issues in Inhalation Therapy. 3) Mild persistent asthma: the case for inhaled corticosteroid therapy

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Abstract

Mild persistent asthma should be treated with continuous inhaled corticosteroids (ICS), which reduces exacerbations of disease, controls symptoms and reduces bronchial mucosal inflammation. Most patients can be controlled with low dosage ICS (≤ 500 mcg/day beclometasone or equivalent) and there is limited benefit from further escalating dosages. There is some evidence of additional benefit of early treatment in terms of better longer term control of symptoms, but not alteration of the natural history of the disease. Withdrawal of ICS therapy results in rapid relapse of symptoms. Although some studies have suggested that intermittent therapy with ICS is not detrimental to asthma control, in the absence of any studies investigating the long term clinical, functional and pathophysiological differences between regular and intermittent therapy, the former continues to be recommended in guidelines. In patients well controlled on low/moderate dosages of ICS there is little benefit of adding any other medication and no rationale for commencing combination therapy routinely as first line controller therapy. There is no evidence that ICS or any other medication prevents the occurrence of asthma, and scanty evidence that the decline in lung function associated with asthma is arrested to any significant degree by ICS therapy. ICS has variable effects on features of airways remodelling but the long term physiological consequences of these effects, if any, are as yet unknown.

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Introduction

Asthma is a clinical syndrome characterised by airway inflammation, variable airway obstruction and airway hyperresponsiveness.[1] Asthma severity is usually classified according to the Global Initiative for Asthma (GINA) classification system[1] or the American National Institutes of Health asthma education and prevention programme EPR3 guideline.[2] The British guideline, published by the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN)[3] does not formally define asthma severity. There are four categories based on clinical and functional features – mild intermittent, mild persistent, moderate persistent and severe persistent.

The standard of care for patients with mild intermittent and mild persistent asthma in the past was intermittent or regular use of inhaled short-acting β_2-agonist therapy respectively. Whilst this is still true for mild intermittent asthmatics, current guidelines[1-3] no longer recommend this for the mild persistent group because of reports of increased risk of death and deterioration of asthma control.[4,5] Regular controller therapy in the form of inhaled corticosteroid (ICS) is now recommended for this group of patients.

This paper – the third in a series of reviews on various inhalation therapy topics being published in this journal by the ADMIT working group (see the first review paper[5a] for individual affiliations and conflict of interest declarations) – will examine aspects of the appropriateness and efficacy of ICS therapy in the management of mild persistent asthma.

ICS for asthma therapy: effects on lung function, symptoms and mortality

ICS monotherapy achieves successful control of mild/moderate persistent asthma in a significant proportion of patients. Generally, the dose-response curve of ICS is relatively flat for a number of outcome measures[6] and for many patients the therapeutic benefits of high-dosage versus low-dosage ICS may be marginal.[6-9] Nevertheless, in the majority of patients, even at low dosages, ICS rapidly improves clinical symptoms and measures of lung function.[10] The anti-inflammatory action of ICS markedly decreases airways hyperresponsiveness[11,12] and in the long term reduces the frequency and severity of exacerbations.[10,13]

The use of ICS on a regular basis also leads to reduced mortality from asthma. Suissa and colleagues[14] used Canadian health data to review a population-based cohort of over 30,000 patients receiving anti-asthma drugs between 1975 and 1991. Subjects who had died from asthma and for whom records were complete (n=68) were matched with 2,681 control subjects within the cohort. Rate ratios for death from asthma were calculated after adjustment for a number of variables. The authors calculated that the death rate from asthma decreased by 21% with each additional canister of ICS used by the patients in the preceding year.

These data and a very large body of additional comparative evidence quoted in all of the above guidelines[1-3] have resulted in concordant agreement that ICS is the most effective current controller therapy for asthma in adults and children of all ages. The EPR3 guidelines[2] further conclude that "studies demonstrate that ICS improves asthma control more effectively in both children and adults than leukotriene receptor antagonists or any other single long-term control medication".

Early intervention with ICS to prevent progression of asthma

In the START study, investigators looked into whether early intervention with ICS prevented progression of asthma in adults and children aged 5-11 years with newly diagnosed mild persistent asthma.[15] A total of 7,241 patients were treated with low-dose budesonide (400 mcg/day for adults or 200 mcg/day for children younger than 11) or placebo for three years. During the first year, almost 34% of individuals in the placebo arm needed rescue treatment with ICS and 4% had had at least one severe asthma exacerbation. By comparison, in the budesonide treated group, only 20% needed additional ICS and 2% experienced severe exacerbations. Compared with placebo, budesonide therapy increased lung function over the course of one year of therapy and further after three years. This study suggests that early treatment with low-dose ICS decreases the risk of severe exacerbations, and improves asthma control and lung function in patients with mild persistent asthma of recent onset. A cost-effectiveness analysis based on these data also favoured early use of ICS.[16] A second report on the START study[17]

presented results of 5-year follow-up of the patients. After the initial 3-year treatment period with placebo or ICS therapy, all patients then went on to receive ICS treatment for two more years in an open label fashion. Over the entire 5-year study period, patients taking ICS in the double-blind phase had a significantly lower risk (odds ratio 61%) of a severe, asthma-related event compared with those taking placebo. Furthermore, these patients overall used less additional medication. The authors concluded that early intervention with ICS in mild, persistent asthma improves asthma control and is associated with reduced usage of additional medications.

In the CAMP study,[11] in which treatment with ICS, inhaled nedocromil and placebo was compared in 1,041 children aged 5-12 years with mild intermittent asthma over a 4-6 year period, ICS therapy was superior to placebo in terms of reducing disease exacerbations, systemic corticosteroid and rescue medication usage, and improving symptom scores. In a smaller study[18] in which 44 adults with mild persistent asthma were randomised to receive inhaled fluticasone 500 mcg/day or placebo for 11 months, fluticasone therapy improved spirometry, airways hyperresponsiveness and reduced exhaled nitric oxide significantly more than placebo. Although there were no significant differences in the usage of rescue medication (which was in any case <2 times/week at the commencement of the study), symptoms or quality of life, fewer patients suffered mild exacerbations taking fluticasone compared to placebo (22% vs 62%) over the duration of the study.

Examination of bronchial biopsies of asthmatics indicates that significant inflammation is present early in the course of asthma, even in those patients having had a short duration of symptoms.[10] Early use of ICS suppresses airway inflammation, improves symptom control and restores pulmonary function.[10,13] A prospective controlled study[19] followed pulmonary function in 216 children during long term treatment with ICS and compared the findings of those with 62 children not so treated. Children who started ICS therapy more than five years following a diagnosis of asthma had significantly lower FEV_1 measurements than those starting it within two years of the onset of asthma. Additionally, children treated with ICS had significantly fewer hospital admissions because of exacerbations and a lower cumulative exposure to corticosteroids in the long term. The effect of early as opposed to delayed ICS therapy has also been studied in patients with asthma symptoms for less than a year with no previous exposure to anti-inflammatory therapy.[20] Over a 2-year period, 50 patients received budesonide at 1200 mcg/day while 50 received terbutaline 500 mcg/dose taken as required. After this period the 37 patients remaining in the terbutaline group were switched to budesonide and results compared again after a further year of therapy. Patients who switched to budesonide did improve but to a lesser degree than those receiving early budesonide therapy. There was a trend for greater improvement in all lung function measures in the patients who received early budesonide treatment. In a similar study,[21] a mixture of patients with asthma and chronic obstructive pulmonary disease (COPD) were treated with ICS and short-acting bronchodilator or short-acting bronchodilator alone for 2.5 years, and then ICS therapy was started in the patients not having previously received it. After a further six months of follow-up, the improvement in FEV_1 was not significantly different in the asthmatics having received ICS for 2.5 years as compared to those having received it for six months after a 2.5 year delay; bronchial hyperresponsiveness did, however, improve significantly more in the former group (histamine PC_{20} 1.7 as compared with 0.79 doubling concentrations, albeit following a treatment period which was 5 times longer).

These studies clearly show that ICS therapy, compared with placebo, reduces symptoms and exacerbations in mild intermittent asthma. They also provide some evidence to support the contention that delay in commencing regular ICS therapy when this is indicated because of symptoms may result in a slower and less extensive subsequent response to therapy, so that ICS therapy should be commenced as soon as justified by such symptoms. This is certainly the line taken by major asthma guidelines and advocated by most physicians in the UK. However, other physicians[22] have pointed out that, in the follow-up to the START study,[17] although patients with mild intermittent asthma taking placebo instead of ICS for three years showed some evidence of delay in "catching up" after two further years of ICS therapy compared with those taking ICS for the full five years, the differences were not all that great – at the end of two years their impairment, symptomatology and risk of exacerbation were no different to those who had received ICS for five years. According to this view, delay in commencing ICS in patients with symptoms that merit them is, while not necessarily desirable, also not necessarily disadvantageous in the longer term.

Withdrawal of ICS in stable mild/moderate persistent asthma

In a small study,[23] 19 patients with stable mild/moderate asthma were randomised into two groups. In the first group ICS was withdrawn and in the other group ICS was continued. 90% of patients in whom ICS was withdrawn relapsed in a mean of 1.55 months compared with 25% in the group in which ICS was continued. Asthma symptom scores and lung function during follow-up over a year were found to be lower in the group where ICS was withdrawn. In a second study,[24] 28 children treated for one year with budesonide (200 mcg three times daily) were randomised to continue treatment or to receive a lower dose of budesonide for two months followed by placebo for four months. In the withdrawal group there were eight exacerbations of asthma compared with none in the group that

continued therapy; in addition, lung function deteriorated and bronchial hyperreactivity increased. Similar findings were observed in a third withdrawal study.[25]

These studies all confirm that withdrawal of ICS therapy in stable asthmatics previously deemed to require it for disease control increases the risk of relapse in the fairly short term. Thus, asthma guidelines[1-3] agree in stressing the point that, while ICS therapy is currently the most effective therapy known for asthma, it is not curative – and if withdrawn when needed, deterioration of clinical control follows typically within weeks to months. On the other hand, these studies do not obviate the obligation of the physician to minimise the dosage of ICS needed to control symptoms in each individual patient: this might include a trial of complete withdrawal of ICS therapy in those whose symptoms become intermittent or disappear.

Daily versus intermittent ICS therapy

In the IMPACT study,[26] a total of 225 adults with long-standing mild persistent asthma underwent a 10-14 day period of "intense combined therapy" with oral prednisolone, inhaled budesonide and oral zafirlukast, and were then randomised to receive inhaled budesonide, oral zafirlukast or daily placebo for one year. In addition to this regular therapy, all patients were instructed to take intermittent, short-course corticosteroid guided by a standard, symptom based action plan. At the end of one year, the ICS-treated patients showed greater improvements in lung function, bronchial hyperreactivity and symptom-free days. There were no differences between the groups in terms of changes in quality of life, numbers of asthma exacerbations or post-bronchodilator FEV_1. In a second study,[27] patients with mild persistent asthma were treated with continuous ICS (budesonide 400 mcg/day), continuous zafirlukast (40 mg/day), or intermittent courses of ICS (budesonide 1600 mcg/day) for 10 days or systemic corticosteroid (prednisone 0.5 mg/kg/day) for five days, again according to a symptom-based action plan. Improvements in morning peak expiratory flow (PEF) and disease exacerbation rates were similar in all three groups, despite the fact that that the patients randomised to intermittent ICS therapy took this for a mean of no more than 0.5 weeks/year. Furthermore, improvements in other outcome measures (pre-bronchodilator FEV_1, bronchial hyperresponsiveness, symptom scores and number of symptom-free days) were better in this group. These studies, along with the question regarding the possible disadvantages of delaying regular ICS therapy in mild persistent asthma (see above) have generated calls[22,28] for guidelines to consider the feasibility and cost effectiveness of intermittent ICS treatment as a possible management option in this group of patients (especially in poor or underdeveloped countries). They have not yet been incorporated into treatment guidelines because of reservations about the longer term effects of intermittent therapy (particularly accelerated decline in lung function even though neither the IMPACT nor the START studies suggested this). However, it is possible that at least some patients with mild persistent asthma may not be disadvantaged by intermittent ICS therapy, which in any case it has been argued better resembles the "real life" situation in which very few patients in practice take controller therapy absolutely regularly at the prescribed dosage.

ICS versus cysteinyl leukotriene receptor antagonist (LTRA) monotherapy for mild persistent asthma

Cysteinyl leukotrienes, produced by a variety of inflammatory cells implicated in asthma, are powerful bronchoconstrictors and also increase mucus secretion and oedema in the bronchial mucosa. They amplify inflammation through their chemo-attractive effects on inflammatory cells such as eosinophils. Consequently, in addition to causing bronchodilatation, leukotriene receptor antagonists (LTRAs) have also been shown to have anti-inflammatory properties in asthma.[29,30] Four studies involving both adults and children with mild persistent asthma compared therapy with LTRA and low-dosage ICS.[31-34] Both drugs improved most asthma outcomes, but ICS was significantly superior in terms of most outcomes (asthma control, lung function and inflammatory biomarkers).

Despite these studies, LTRAs are widely used outside the UK as monotherapy for mild, persistent asthma, especially in children. Furthermore, guidelines are curiously ambivalent about the use of LTRA as monotherapy instead of ICS in mild persistent asthma. The GINA guideline[1] states that LTRAs "may be used as an alternative treatment for adults with mild persistent asthma" but also that "when used alone as a controller the effects of LTRA are less than those of ICS and, in patients already on ICS, LTRA cannot substitute for this treatment without risking the loss of asthma control".[35,36] For children, no specific comment is made about their use as monotherapy, although it is stated that "LTRA provide clinical benefit in children at all levels of severity but less than that of low dose ICS".[31,37] The EPR3 guidelines,[2] based on evidence from five placebo-controlled trials,[31,32,37-39] state that "patients who have mild or moderate persistent asthma and are treated with ICS, compared to other single long term control medications, demonstrate greater improvements in pre-bronchodilator FEV_1, reduced airway hyperresponsiveness, symptom scores, exacerbation rates and symptom frequency, as well as less use of supplemental SABA [short-acting β_2-agonist], fewer courses of oral systemic corticosteroids, and less use of hospitalisation" but nevertheless conclude that, in both adults and children, LTRA monotherapy is an "alternative, not preferred" treatment. The BTS/SIGN guideline[3] states that LTRA therapy is "less effective" than ICS as monotherapy and suggests that LTRA might be used in children <5 years old in whom ICS "cannot be used". Notwithstanding this, most clinicians would

have to conclude from all of these studies that LTRA should be used as monotherapy for mild persistent asthma only as a last resort when ICS cannot, for whatever reason, be used. The reasons for the continuing popularity of LTRAs as monotherapy in practice in some countries are not clearly defined but may relate to perceived problems with giving ICS to children or using inhaler devices in this age group.

ICS versus theophylline monotherapy for mild persistent asthma

Theophylline is a rather weak, non-specific inhibitor of phosphodiesterase which elevates cyclic AMP concentrations in airway smooth muscle and immune cells, resulting in modest bronchodilatation and inhibition of inflammatory cells. Theophylline has limited effectiveness when given as monotherapy in adult asthmatics[40] but is more effective than placebo at relieving symptoms in children.[41] Several studies have shown that ICS is more effective than theophylline for monotherapy of mild, persistent asthma. For example, in a randomised parallel group study of 74 patients with mild persistent asthma, patients were treated with inhaled budesonide 400 mcg/day, oral montelukast 10 mg/day or sustained-release theophylline 400 mg/day for three months. The patients treated with ICS showed significantly greater improvement in lung function as compared with those treated with both alternative medications, although the changes in FEV_1 and PEF did not exceed the baseline variability. Asthma symptoms and the use of rescue medication were similar in all three groups.[42] Cochrane meta-analysis to determine the efficacy of xanthines such as theophylline in the maintenance treatment of children with asthma[43] demonstrated that they are less effective in preventing exacerbations as compared with ICS but as effective as monotherapy with regular inhaled short-acting β_2-agonist and cromoglicate for treating mild, intermittent disease. Consequently all major guidelines, while acknowledging the activity of theophylline, agree that it is less effective than ICS monotherapy for mild, intermittent asthma. In addition the EPR3 guideline[2] states that theophylline is "not recommended" in children 0-4 years of age owing to its "erratic metabolism during viral infections and febrile illness" and is "less desirable" in 5-11 year olds because of its "safety profile" although it may be contemplated when "cost and adherence to inhaled medications are concerns".

In summary, these data show that early intervention with ICS decreases the risk of severe exacerbations and improves asthma control in mild persistent asthma of recent onset. ICS therapy is superior to LTRA and xanthine therapy, at least within the relatively short term scope of clinical trials, for control of asthma and improvement of lung function. While intermittent, symptom-led therapy may be suitable for some patients with mild persistent asthma, this is not yet advocated in any major guidelines, and cannot be generally recommended until further long-term studies are available.

Corticosteroid resistance

Despite the generally favourable response of mild, persistent asthmatics to ICS therapy, as with all drugs there is a spectrum of response and there will be some patients who require more than an "acceptable" dose of ICS (beclometasone or equivalent ≤800 mcg/day in adults, ≤400 mcg/day in children) to achieve symptom control. Before coming to this conclusion the physician should review, and eliminate where possible, external factors which may be upsetting asthma control in individual patients (allergens, including food allergens in children and occupational allergens, concomitant untreated rhinosinusitis, drugs such as β-blockers and non-steroidal anti-inflammatory drugs such as aspirin). By far the commonest causes of "non-responsiveness" to therapy are, however, poor inhaler technique and poor compliance.

Relative resistance to ICS therapy may also be a consequence of particularly severe or unusual types of airways inflammation in asthma[44] or, at least in theory, structural changes refractory to reversal by corticosteroids. A number of environmental factors may affect the responsiveness of T cells and other inflammatory cells in asthma to corticosteroid inhibition;[45] an important one is cigarette smoking, which reduces clinical responsiveness to ICS in mild asthma[46] and should be discouraged.

Ultimately all patients are likely to show at least some response to ICS therapy although in a minority the dosages required may be relatively high. With such patients, physicians should weigh the problems of unwanted effects of the drugs against optimisation of quality of life, whilst minimising co-morbidity that may compromise asthma control and encouraging good inhaler technique and compliance with dosing regimens.

Beyond ICS alone: other therapeutic options

(1) Addition of long-acting β_2-agonist (LABA)

In adults with mild persistent asthma insufficiently controlled with moderate dosages of ICS, all guidelines agree that adding in a LABA, rather than further increases in ICS dosage, is the preferred initial course of action. Addition of a LABA to a daily regimen of ICS reduces day and night symptoms, improves lung function, reduces rescue medication usage, reduces exacerbations, and achieves clinical control of asthma in more patients, more rapidly and at a lower final dosage of inhaled ICS than increased dosages of ICS given alone.[47-53] There is a paucity of studies on the effects of LABA in children, particularly under the age of 5 years: while the BTS/SIGN guideline[3] still recommends LABA as the first line add-on therapy to ICS in children over the age of 5 years, the GINA guideline[1] suggests LTRA as an alternative, while the EPR3

guideline[2] concludes that there is insufficient evidence at present to know whether adding in a LABA or increasing ICS dosage is best. All guidelines agree that LABA should never be given without ICS. This follows a study[54] showing a small but significant excess of deaths in asthmatics receiving daily treatment with salmeterol compared with placebo added to their usual asthma therapy (13/13,176 patients taking salmeterol compared with 3/13,179 patients taking placebo). The MHRA and the BTS, following a long review of the evidence, concluded that LABA can still be used provided they are given with ICS (the implication being that masking of symptoms with LABA while avoiding ICS is potentially dangerous). For this reason, combination inhalers containing ICS and LABA, although no more or less effective than taking the two drugs in separate inhalers, are preferable when prescribing a LABA because they ensure that LABAs can never be taken without ICS.

Notwithstanding this evidence, it is important to note that many patients with mild, persistent asthma are adequately controlled on ICS alone. In these patients, adding in a LABA is of no additional benefit. The BTS/SIGN guideline[3] states that "in patients on ICS whose asthma is stable, no intervention has been consistently shown to decrease ICS requirement in a clinically significant manner compared to placebo". As an illustration of this, the OPTIMA trial[55] sought to establish whether adding a LABA (formoterol) to ICS (budesonide) in mild and moderate persistent asthmatics would reduce exacerbations. Both children (older than 12 years) and adults were included as long as post bronchodilator FEV_1 was ≥80% of the predicated value. The prevalence of severe asthma exacerbations was reduced and symptom scores improved in the mild persistent asthmatics treated with budesonide as compared with a placebo-treated group over a year of therapy. The combination of budesonide and formoterol did not provide any additional benefit in this group. In contrast, in the group with moderate persistent asthma using ICS at the beginning of the study, a significant reduction in asthma exacerbations was seen when formoterol was added to budesonide. These findings emphasise the fact that patients with mild, persistent asthma well controlled on ICS alone do not need anything else. Similarly, in a Cochrane meta-analysis,[56] the effects of initiating therapy with ICS alone as compared with ICS and LABA were compared in steroid-naïve adults and children with mild persistent asthma. The addition of LABA to ICS did not significantly reduce the rate of exacerbations or use of rescue medications as compared with patients treated with ICS alone. Consequently, physicians should not be tempted to use combination therapy too hastily.

(2) Addition of leukotriene receptor antagonist (LTRA)

Several studies have suggested that LTRA are sparing of ICS. For example, in a double blind controlled study of asthmatics still symptomatic despite taking moderate to high dosages of budesonide (400-1600 mcg/day), the addition of montelukast 10 mg/day was shown to improve symptoms, reduce the use of rescue medication and improve lung function as compared with placebo.[57] In a second double-blind, randomised study on similar patients inadequately controlled on budesonide 800 mcg/day, addition of montelukast 10 mg/day was shown to produce outcomes (improvement in symptoms, quality of life and lung function) equivalent to doubling the dosage of inhaled budesonide.[58]

A Cochrane meta-analysis comparing the addition of LABA to LTRA in asthmatics inadequately controlled on moderate to high dosages of ICS suggested that LABA was superior to LTRA in preventing exacerbations requiring systemic steroid therapy, improving lung function and reducing symptoms and the use of rescue medication.[59] Thus the major guidelines recommend LABA as a first-line add-on therapy before LTRA in adults and older children, although in infants, in whom there is a paucity of evidence of the effectiveness of LABA, LTRA would seem a more legitimate alternative.

In conclusion, while the benefits of adding in LABA (and to a lesser extent LTRA) in patients with asthma with good compliance and perfect inhaler technique whose disease is not controlled with low/moderate dosages of ICS are manifest, it is unnecessary and wasteful to use these drugs in patients whose control is adequate on acceptable dosages of ICS alone.

Management of mild intermittent asthma

There are many fewer data addressing the optimal treatment for patients with mild intermittent asthma since they remain relatively well and have very infrequent symptoms. Current guidelines recommend intermittent short-acting bronchodilator for this group of patients. The SOMA study[60] compared as-needed use of LABA with as-needed use of LABA/ICS combination therapy as the only medication in a group of patients with mild intermittent asthma. The frequency of asthma-free days was similar in the two groups; however, compared with the LABA-only group, significantly fewer patients in the ICS/LABA-treated group needed more than four puffs of "as required" short-acting reliever on any day. The results of this study cannot be extrapolated to all patients with mild intermittent asthma, since the patients were selected on the basis of having high exhaled nitric oxide (thought to be a biomarker of active airways inflammation). Furthermore, the situation has been coloured by anxiety about prescribing LABA in the absence of ICS (see above). The long-term implications of this particular treatment strategy in terms of benefit/risk are therefore unknown. Similarly, there is a paucity of evidence examining the benefit/risk implications of long-term ICS therapy in patients with mild intermittent asthma. Current evidence-based guidelines suggest the use of intermittent short-acting bronchodilators for this patient group, and at present there is insufficient evidence to overturn this conclusion.

Does ICS therapy prevent asthma?

Studies of whether ICS therapy prevents asthma, at least in children, are potentially confounded by the fact that at least half of pre-school wheezing children will stop wheezing by the time they start school.[61] Indeed, there is some debate as to whether any pre-school wheezy children should ever be treated with ICS.[62]

In the PAC study,[63] infants (aged 1 month to 3 years) of mothers with asthma were treated with ICS (budesonide 400 mcg/day) or placebo using a metered-dose inhaler and spacer device starting on day 3 of any wheezy episode and continued for two weeks. Children discontinued the trial if they developed persistent wheezing (more than five episodes lasting three days within a 6-month period, or daily symptoms for more than four weeks). Two hundred and ninety-four children, mean age 10.7 months, were randomised. Intermittent ICS therapy had no effect on the progression from intermittent to persistent wheeze, which was observed in 24% of the ICS treated group and 21% of the placebo treated group.

In the IFWIN study,[64] 206 older children aged 6 months to 5 years with at least one atopic parent were given ICS (fluticasone 100 mcg twice daily) or placebo after one prolonged (>1 month) episode of wheezing or two physician-confirmed wheezy episodes. The dosage was adjusted every three months to the minimum required to control symptoms. At the age of 5 years there was no difference between the groups in the proportion of children with current wheeze, physician-diagnosed asthma or usage of asthma medication.

In the PEAK study,[65] 285 2-4 year olds considered at risk of asthma were randomly assigned to receive ICS (fluticasone propionate 88 mcg twice daily) or placebo using a metered dose inhaler and spacer for two years. They were then followed for a further observational year. During this year there were no significant differences between the groups in terms of symptom-free days or exacerbations of wheeze.

All of these studies, although directed at slightly different patient populations (all of them children) and with slightly different criteria for "risk of asthma", seem to lead to the same conclusion, namely that ICS therapy does not prevent asthma. They also underline the difficulty with diagnosing asthma and distinguishing it from virus-induced wheezing in this age group. The BTS/SIGN guideline[3] states that suggestive symptoms (wheeze, cough, difficulty breathing, chest tightness), particularly if frequent and recurrent, worse at night and early in the morning, triggered by stimuli such as exercise, emotion and allergen exposure, and occurring apart from colds, increase the probability of a diagnosis of asthma in children, as does audible wheeze on chest auscultation and a personal or family history of atopic disease (eczema, allergic rhinitis, food allergy, asthma). On the other hand symptoms only with colds, isolated cough and normal chest examination and spirometry during symptoms reduce the probability of asthma.

Most children with wheeze presenting before the age of 2 years become asymptomatic by mid-childhood and do not need treatment. Symptoms present from birth, severe upper respiratory tract disease, persistent moist cough, excessive vomiting, dysphagia, stridor, abnormal voice or cry, focal signs in the chest, finger clubbing and failure to thrive all lower the probability of asthma and suggest an alternative diagnosis. Lung function testing adds little information in children under the age of 5 years. For children in whom the probability of asthma is considered high, a trial of ICS therapy for 2-3 months followed by reassessment is indicated. A good symptomatic response strongly supports the diagnosis, whereas a poor response is very much against it. For children in whom the probability of asthma is considered to be lower, a period of watchful waiting is reasonable along with possible further investigation for unusual symptoms or signs. Physicians should be mindful of the importance of not missing, but nevertheless firmly making, a diagnosis of asthma before committing a child to long term therapy, and can be reassured that in this situation delay in commencing ICS therapy does not appear to alter the risk of the child developing chronic disease.

Does ICS therapy prevent lung function decline in asthma?

The natural history of lung function is that it increases during childhood, reaches a peak during early adulthood (25-35 years) and then slowly declines with age. The evidence is that children who wheeze persistently at the age of 6 (many of whom will go on to develop chronic asthma) have impaired lung function which was nevertheless normal at birth.[66] In contrast, children under 2 years of age who wheeze with colds (most of whom do not go on to develop asthma) have diminished lung function in infancy which tends to improve (though not always completely) by the age of 6 years.[66] There are few studies which have followed lung function in asthmatics over protracted periods of time, but one such study suggested that middle aged asthmatics with significant airways obstruction already had reduced lung function at the age of 10 years.[67] Taken together, these studies could be interpreted as showing that children who are going to develop chronic asthma start off in life with normal lung function which deteriorates during childhood and never recovers. Several studies[68,69] have shown that lung function in adult asthmatics (and most particularly the degree of reversibility of airways obstruction as measured by post-bronchodilator FEV_1) declines substantially faster compared with non-asthmatics. Consequently there is interest in blocking this early decline in lung function in asthmatics, in the hope that it will bring long-lived symptomatic benefit with less treatment.

The first study to suggest that ICS may inhibit lung function decline in asthma was directed primarily towards effects of ICS on child growth.[19] It was noticed that the annual increase in

pulmonary function in a group of child asthmatics was significantly accelerated after commencing budesonide as compared with the run-in period, and also as compared with a group of untreated controls. The extent of the improvement with budesonide was noted to depend on how long the budesonide treatment was started after the onset of asthma symptoms.

In the CAMP study,[11] children aged 5-12 years with mild/moderate asthma were treated from 4-6 years with budesonide 200 mcg twice daily and compared with a group treated with placebo and taking reliever medication and prednisolone only when needed. There was no significant difference in the change in lung function (post-bronchodilator FEV_1) in each group. As compared with the children assigned to placebo, however, those treated with budesonide showed a significantly smaller decline in pre-bronchodilator FEV_1/FVC ratio and improved airways hyperresponsiveness, suggesting that their asthma was better controlled but their overall lung function no different.

In addition, the three studies in pre-school wheezy children described above[63-65] all examined changes in lung function as additional outcome measures. None of these studies demonstrated any significant difference in changes in lung function in children treated with ICS as compared with placebo therapy using various techniques of measurement.

In the START trial,[15] which involved over 7,000 patients with mild intermittent asthma not previously treated with regular inhaled ICS who were randomised to receive ICS therapy or placebo for three years, post-bronchodilator FEV_1 had declined significantly less in the patients treated with ICS as compared with those treated with placebo, although the difference was extremely small. In the follow-up phase of this study,[17] when all patients were treated with ICS for a further two years, post-bronchodilator FEV_1 had declined by a small (mean 2.22%) but equivalent degree in all patients, irrespective of whether or not they had received ICS in the randomised, double-blind phase. In the IMPACT study,[26] in which 225 adults with mild persistent asthma were randomised to receive twice daily budesonide (200 mcg), zafirlukast (20 mg) or placebo, there were no significant differences in post-bronchodilator FEV_1 after a year of therapy between the groups.

Consequently it must be concluded that, whilst ICS therapy is very effective in mild persistent asthma for controlling symptoms and improving lung function, there is no clear evidence that it prevents the early lung function decline which is surmised to herald further deterioration later in life. It is perhaps worth noting that these studies - at the population level, and in relatively small numbers of patients - are unlikely to unearth a possible subgroup of asthmatics whose lung function deterioration is slowed by ICS therapy.

ICS and airway remodelling

Airway remodelling is the collective term used to describe structural changes seen in the airways of asthmatics which comprises epithelial damage, deposition of structural proteins below the reticular basement membrane (subepithelial fibrosis), bronchial smooth muscle hypertrophy and hyperplasia, hyperplasia of mucous glands, and increased mucosal vascularity. The reason for the interest in these features is that they have been postulated to contribute to the accelerated decline in lung function and irreversibility of airways obstruction associated with asthma. At present there are problems with this interpretational scenario. Although intuitively these changes might be surmised to contribute to irreversible changes in airway function, there is as yet little or no direct evidence that they actually do so. They are widely assumed to be brought about by mediators released by inflammatory cells. Whilst it is true that certain cytokines, such as transforming growth factor beta (TGF-β) and interleukins such as IL-11 and IL-17 can cause bronchial mucosal fibroblasts to secrete fibrotic proteins such as collagen, while others such as IL-13 can promote mucous gland hypertrophy in cultured bronchial epithelial cells, there are still many doubts about the cause and effect relationship between inflammation and remodelling, not least because it is so difficult to characterise the natural histories of the two phenomena. Of the few studies in children, some have reported that severe asthma is associated with airways remodelling[70,71] whereas others[72] suggest that remodelling changes predispose to, but pre-date, clinical asthma. Such studies cast doubt upon the tenet that remodelling is caused by inflammation and in turn contributes to asthma symptoms and physiology. In both children and adults, remodelling changes have been linked to asthma severity but not always longevity,[70,71,73] suggesting that they are not necessarily cumulative, and possibly reversible with time.

Boulet and colleagues[74] examined bronchial biopsies in 32 adult asthmatics, 16 of whom had been recently diagnosed with asthma and 16 of whom had long-standing asthma, both before and after eight weeks of therapy with inhaled fluticasone propionate 1000 mcg daily. Baseline sub-epithelial collagen deposition was similar in both groups and this did not alter significantly following the high dose ICS therapy. However, a second study[75] did show significant reduction in the thickness of the sub-epithelial reticular layer in a group of asthmatics whose ICS dosages were increased according to their degree of bronchial hyperresponsiveness as compared to a comparison group where dosages were adjusted to standard asthma guidelines.

With regard to mediators of remodelling, one study[76] showed no effect of systemic corticosteroid therapy on the expression of TGF-β, considered a key remodelling cytokine, in airway biopsies of moderate to severe asthmatics. It was noted, however, that expression of IL-11 and IL-17 was markedly reduced. *In vitro*, IL-17 stimulates fibroblasts to produce IL-6 and IL-11, both of which are pro-fibrotic.[77] These effects are therefore variable and it is not

possible to form an overall impression from these studies of the net effects of ICS therapy on airways remodelling.

Orsida and colleagues[78] demonstrated significantly increased vascularity of the lamina propria in steroid-naïve asthmatics compared with normal controls and asthmatics taking ICS. Similarly, Feltis and colleagues[79] showed that treatment of asthmatics with ICS for three months significantly reduced the cross-sectional area of vessels in bronchial biopsy specimens as compared with a placebo-treated group. The expression of vascular endothelial growth factor was also reduced in the biopsies but not within the lumen of the airways.

In summary, it would appear that there is a degree of reversibility in at least some of the processes involved in airways remodelling with ICS, although the effects are complex and interpretation is confounded by lack of knowledge of the natural history of these processes and understanding of their contribution to symptoms and airways physiology in chronic asthma. At present this has generated disparate views as to the importance of commencing ICS therapy as early as possible in asthma. Some authors argue that ICS therapy should be started as soon as possible after asthma is diagnosed to prevent (at least some) remodelling changes,[72] whereas others hold that the case for early inhibition of remodelling is unproven and does not of itself justify early commencement of ICS therapy.[80] The most recent evidence,[81,82] albeit from relatively small numbers of subjects, suggests that there does not appear to be increased inflammatory cellular infiltration or submucosal protein lay down in wheezy infants up to 26 months of age with or without measurable airways obstruction, whereas such changes start to become detectable in 1-3 year olds with severe, persistent wheeze. Taking account of these and other findings, the EPR3 guideline[2] concludes that the evidence does not suggest that "early intervention with an ICS…alters the underlying severity or progression of the disease" so that "ICS should be used to control asthma symptoms and to improve the child's quality of life, but their use should not be initiated or prolonged for the purpose of changing the natural history of the disease".

Addendum
The ADMIT Working Group

ADMIT is a consortium of European respiratory clinicians with special expertise in inhalation therapy who review published evidence to examine ways of improving the treatment of obstructive pulmonary airway diseases in Europe. ADMIT is supported by an unrestricted educational grant from MEDA AB. Members of ADMIT receive a small honorarium from MEDA AB for attending meetings, and travel expenses are reimbursed. See the first ADMIT paper published in this journal in December 2007 for a full list of individual conflict of interest declarations.[5a]

Conflict of interest declaration

Mark Levy is the Editor-in-Chief of the *PCRJ*, but was not involved in the editorial review of, nor the decision to publish, this article.

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