Pharmacotherapy of asthma: regular treatment or on demand?

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***Abstract*:** Some studies have raised the question of the need for chronic controller therapy in mild persistent asthma as suggested by international guidelines. Although the Improving Asthma Control (IMPACT) and Beclomethasone plus Salbutamol (BEST) studies suggest that on-demand therapy in some patients with mild persistent asthma achieves a similar degree of asthma control based on symptoms and functional outcomes, the IMPACT study indicates that regular and on-demand therapy is not equivalent for controlling airway inflammation. Persistent airway inflammation might lead to airway remodelling with onset or worsening of symptoms, deterioration in lung function, and reduced response to pharmacological therapy. However, the relationships between chronic airway inflammation and airway remodelling need to be clarified. Choosing the 'right' pharmacological strategy (regular *versus* on-demand treatment) for asthma control is currently difficult due to the fact that (1) inflammatory outcome measures were not generally incorporated into asthma clinical trials; (2) the relationships between chronic airway inflammation and airway remodelling are largely unknown; (3) current clinical asthma trials that are generally based on symptomatic and functional outcome measures are too short to assess the impact of regular anti-inflammatory therapy on natural history of asthma; (4) asthma is an heterogeneous disease and different phenotypes of asthma patients likely requiring a different therapeutic approach can be identified, even in the same class of asthma severity. Guidelines for asthma management are valuable tools, although they are necessarily based on a strategy directed to the best outcome in a group of patients. Asthma phenotyping is becoming central for asthma management. The issue of regular *versus* on-demand treatment of intermittent and mild persistent asthma would be better addressed if considered within an individualized approach to asthma management and assessment. Identification of clinical, functional, morphological and biochemical phenotypes of patients with asthma and its clinical implications is likely to lead to a tailored, individualized, pharmacological therapy and asthma management.

***Keywords*:** asthma, regular pharmacological therapy, on-demand pharmacological therapy, airway inflammation, inhaled corticosteroids, leukotriene receptor antagonists, long-acting beta agonists

Introduction

Pharmacological treatment is the mainstay of management in most patients with asthma. The primary goals of treatment of asthma are relief of symptoms, normalization of pulmonary function, prevention of acute exacerbations, reduction of airway hyper-reactivity, and improvement of quality of life (Figure 1). A primary objective is to prevent airway remodelling; that is, structural changes in the airways, by preventing the putative long-term consequences of airway inflammation. However, the evidence that supports the concept that pharmacological control of airway inflammation positively influences the natural history of asthma is currently inadequate partially due to relative short duration of clinical asthma trials.

Different long-term control medications including inhaled corticosteroids (ICSs), leukotriene receptor antagonists (LTRAs), long-acting beta agonists (LABAs), chromones, and theophylline, are used daily for asthma control according to international guidelines such as those provided by the National Asthma Education and

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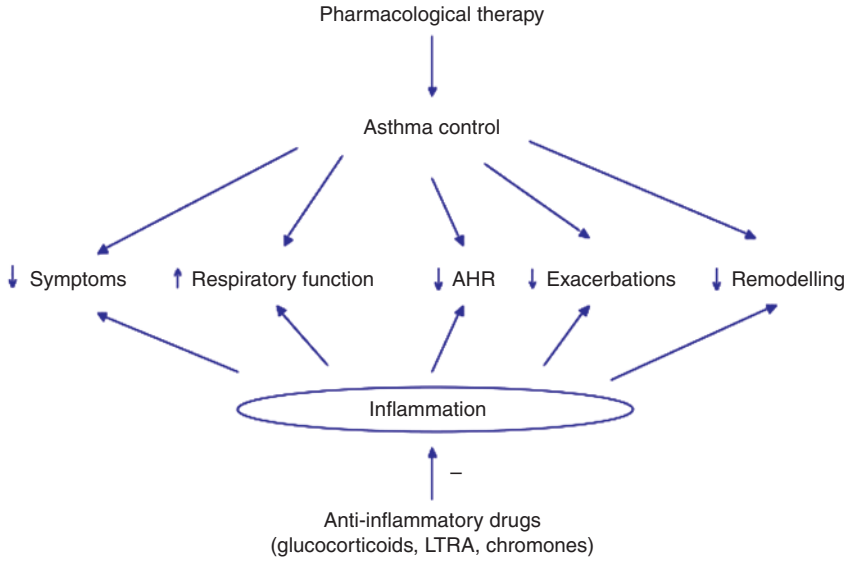

Figure 1. Objectives of the pharmacological therapy of asthma. AHR, airway hyper-responsiveness; LTRA, leukotriene receptor antagonist.

Prevention Program (NAEPP) [NAEPP, 2007] and the Global Initiative for Asthma (GINA) [GINA, 2008].

Pharmacotherapy of asthma is characterized by a stepwise approach based on increasing medications until asthma is controlled, and decreasing medications when possible to minimize side effects. In general, the intensity of treatment should match the severity of symptoms. As a result, patients with infrequent and mild symptoms should be treated intermittently whereas patients with symptoms which are persistent should receive long-term controller medications [GINA, 2008; NAEPP, 2007]. There is now evidence that regular use of ICS is associated with improvements in symptoms and lung function, and with reductions in exacerbation rate, hospitalizations and deaths from asthma [Lazarus, 2006]. However, the threshold for initiating ICS is not evidence-based and the concept that airway remodelling is evitable in patients who take ICS regularly is not fully elucidated [Lazarus, 2006]. In the last few years, some reports have raised the question about the need for chronic controller therapy in mild persistent asthma [Papi *et al.* 2007; Lazarus, 2006; Boushey *et al.* 2005]. This review article, focused on regular or on-demand treatment of intermittent and mild persistent asthma, discusses the possible pharmacological strategies for asthma control in patients with mild disease and presents the principal pharmacological aspects of antiasthmatic drugs.

Antiasthmatic drugs

Short- and long-acting beta agonists, corticosteroids, LTRAs, chromones, methylxantines, anticholynergic antimuscarinic drugs, monoclonal anti-immunoglobulin E (IgE) antibodies are used for pharmacological therapy of asthma. They can be classified both on the basis of their bronchodilator and/or anti-inflammatory effects or on the basis of their roles as quick relief or long-term control antiasthmatic drugs. Inhaled short-acting beta agonists (SABAs) are generally the most effective drugs for quick relief of asthma symptoms and can be used for preventing exercise-induced bronchoconstriction. Combination of inhaled antimuscarinic drugs with a SABA has an additive effect during acute asthma exacerbations. However, antimuscarinic drugs are not effective for chronic pharmacological therapy of asthma and will not be discussed further in this article. ICS are the most effective drugs for long-term control of persistent asthma. Oral LTRAs can be used as monotherapy in mild persistent asthma or as add-on therapy in moderate and severe asthma [Montuschi *et al.* 2007]. Inhaled chromones and oral theophylline have similar indications [NAEPP, 2007], but they are used less frequently. Omalizumab, a humanized monoclonal anti-IgE antibody that is administered subcutaneously, is approved for treatment of severe allergic asthma that is not adequately controlled by other antiasthmatic drugs [Holgate *et al.* 2009; Humbert *et al.* 2005].

Beta agonists

Inhaled beta agonists are the most effective bronchodilating drugs for asthma. The short-acting nonselective (β_1 and β_2) adrenergic agonist isoproterenol (isoprenaline) was initially used, followed by the short-acting selective adrenergic β_2 agonists salbutamol, fenoterol and terbutaline, and subsequently the long-acting selective β_2 adrenergic agonists salmeterol and formoterol.

Inhaled SABAs have rapid onset of action (within 5 minutes) and intermediate duration of effect (from 4 to 6 hours). The inhaled route of administration is preferred because of the more rapid onset of action, maximal bronchodilation and minimal side effects [Nelson, 1995]. At therapeutic doses, tremor is the most common side effect, whereas tachycardia and palpitations are observed mainly at higher doses. The latter effects can result from concomitant activation of cardiac β_2 adrenergic receptors and β_1 adrenergic receptors as selectivity is reduced at high doses. Inhaled SABAs should be used for the relief of acute symptoms. Patients with infrequent and mild symptoms of asthma are best treated with an inhaled SABAs on demand. SABAs do not treat the airway inflammation underlying asthma and are useful in the treatment of symptoms only.

LABAs including salmeterol and formoterol have a duration of action of at least 12 hours which makes them suitable for a regular twice-daily dosing regimen [Lipworth, 2007]. Formoterol, which is a full and not a partial agonist like salmeterol, has a faster onset of action than salmeterol and can also be used to relieve acute bronchoconstriction [Lipworth, 2007]. These medications are classified as long-term controllers; however, they should always be used in combination with a concomitant anti-inflammatory agent, preferably an ICS [Fanta, 2009; Kramer, 2009]. LABAs are currently indicated as an add-on bronchodilator therapy to low-to-medium-dose ICS, especially in acute asthma exacerbations, as showed in a large multicentre controlled trial [Masoli *et al.* 2005]. Several randomized clinical trials confirm that the addition of a LABA to low-medium dose ICS is more effective than increasing the dose of the ICS in controlling moderate-to-severe asthma [Greenstone *et al.* 2005; Bateman *et al.* 2004; Pauwels *et al.* 1997; Woolcock *et al.* 1996]. The molecular mechanisms underlying the apparent additive effect of LABA and ICS on asthma control remain to be fully clarified [Kips and Pauwels, 2001]. However, *in vitro* studies have shown that corticosteroids improve beta-receptor-mediated signalling in the lung, and beta agonists enhance the transcription of genes under the influence of corticosteroids [Giembycz *et al.* 2008]. On the other hand, according to a recent meta-analysis, LABA therapy does not appear to have by itself any clinically important anti-inflammatory or pro-inflammatory effect as showed by the lack of changes in inflammatory cell counts of sputum, BAL or bronchial mucosa in adults and children treated with LABAs [Sindi *et al.* 2009]. Monotherapy with LABA is inferior to monotherapy with ICS as maintenance treatment in persistent asthma [Holgate, 2001; Kips and Pauwels, 2001] and should be avoided due to safety concerns [Kramer, 2009].

Combining beta agonists with ICS is an attractive therapeutic option because ICS suppress the underlying inflammatory response while the chronic use of the beta agonist provides enough symptom control to permit lower dose of ICS to be used. In patients already receiving ICS and whose asthma is not well controlled, the addition of a daily LABA reduced the risk of exacerbations, improved forced expiratory volume in one second (FEV_1) and the number of symptom-free days in comparison with ICS monotherapy [Greenstone *et al.* 2005; Ni Chroinin *et al.* 2005]. Two double-blind controlled trials have evaluated combination therapy: in the former, asthma control was achieved more rapidly and at a lower ICS dose in patients receiving salmeterol plus fluticasone than in patients receiving fluticasone monotherapy [Bateman *et al.* 2004]; in the latter, patients receiving budesonide/formoterol for both maintenance and rescue therapy had lower exacerbation risk, improved symptoms and better lung function than patients receiving rescue terbutaline plus maintenance budesonide/formoterol or rescue terbutaline plus maintenance budesonide [O'Byrne *et al.* 2005]. Finally, several studies have shown the efficacy of LABAs as corticosteroid-sparing agents [Gibson *et al.* 2005; McIvor *et al.* 1998]: addition of a LABA permitted 37–60% reduction of the ICS dose without deterioration of asthma control [Gibson *et al.* 2005].

Safety is a relevant issue in the pharmacology of LABAs [Kramer, 2009; Nelson *et al.* 2006]. In general, controversies about the chronic use of beta agonists in patients with asthma are based upon two arguments: first, mortality may be

increased; second, control of asthma may worsen.

An association between mortality and chronic treatment with SABAs in asthmatic patients was initially suggested by several studies [O'Byrne and Kerstjens, 1996; Spitzer *et al.* 1992; Sears *et al.* 1990]. The risk of death was significantly elevated even after controlling for the severity of asthma [Ernst *et al.* 1993]. However, a meta-analysis found a weak, clinically not relevant association between death from asthma and inhaled SABAs [Mullen *et al.* 1993]. LABA monotherapy may be associated with severe asthma exacerbations and increased mortality [Kramer, 2009]. However, safety of ICS/LABA combinations could be different as concurrent use of ICS might diminish or prevent the negative effects of LABAs [Kramer, 2009]. The Salmeterol Multicenter Asthma Research Trial (SMART) was a double-blind, randomized, placebo-controlled study in which 26355 asthmatic patients were randomly assigned to receive either salmeterol or placebo for 28 weeks added to usual asthma care [Nelson *et al.* 2006]. In patients receiving salmeterol, respiratory-related and asthma-related deaths and combined asthma-related death or life-threatening experiences were significantly increased [Nelson *et al.* 2006]. Subgroup analysis suggested that the risk may be greater in African-Americans compared with Caucasian subjects [Nelson *et al.* 2006]. This study was not designed to evaluate subgroups that did or did not receive ICS. A meta-analysis found that the use of salmeterol combined with fluticasone in patients with persistent asthma did not alter the risk for asthma-related hospitalizations, did not affect risk for asthma-related deaths or asthma-related intubations, and reduced the risk for severe asthma exacerbations when compared with fluticasone alone [Bateman *et al.* 2008]. ICS seem to reduce the potential risk of salmeterol.

Formoterol has not been as well studied as salmeterol. In a prospective study, 2085 asthmatic patients were randomly assigned to receive formoterol in high and low doses and placebo twice-daily for 16 weeks and no difference was found among groups in the incidence of fatal or near-fatal asthma-related events [Wolfe *et al.* 2006]. However, the study duration of 16 weeks may not have been adequate to definitively assess the outcome. Moreover, a trend towards excess mortality in asthma has been reported for formoterol [Sears *et al.* 2009]. The mechanism underlying this effect of the regular use of beta agonists is unknown but a role of the neurotrophin brain-derived neurotrophic factor (BDNF) has recently been postulated [Lommatzsch *et al.* 2009]. BDNF is a mediator of airway hyper-responsiveness (AHR) in asthma; its systemic concentrations are increased in asthmatic patients and these concentrations correlate with AHR [Lommatzsch *et al.* 2005]. Monotherapy with salmeterol significantly increased BDNF concentrations in serum and platelets in a small sample of asthmatic patients and deterioration of AHR was associated with this effect [Lommatzsch *et al.* 2009]. Augmented BDNF could explain some of the adverse effects of beta agonists in asthma [Lommatzsch *et al.* 2009]. However, desensitization of the β_2-adrenergic receptor following continuous exposure to LABAs could explain the observed increase in bronchial reactivity and asthma exacerbation rate. Further studies are needed to clarify whether LABA therapy is associated with an increased risk of fatal asthma exacerbations, its mechanism of action and whether ICS therapy is protective.

A possible adverse outcome found in patients using beta agonists on a regular schedule could be a diminution of the bronchoprotective effect; that is, the ability to protect against bronchoconstriction in response to exercise, allergen exposure and chemical stimuli such as methacholine [Salpeter *et al.* 2004]. This phenomenon, whose clinical significance is debated, may be related to desensitization of the β_2-adrenergic receptor caused by reduced receptor numbers (down-regulation) together with uncoupling of the β_2-adrenergic receptor (ADRB2) from the G protein adenylyl cyclase [Lipworth, 2007]. In addition, 24-h occupancy of receptors by regular exposure to twice-daily salmeterol results in the relative antagonism of salbutamol when the latter is used for rescue treatment of acute episodes of bronchoconstriction [Lipworth, 2007; Grove and Lipworth, 1995]. Like salmeterol, formoterol appears to induce tolerance to the bronchodilating effect of salbutamol [Haney and Hancox, 2005]. However, the clinical significance of the tolerance remains speculative and one study demonstrated that, despite the development of a loss of bronchoprotection, no loss of asthma control occurred as measured by respiratory symptoms [Boulet *et al.* 1998]. Further complicating this issue, the response to treatment

with beta agonists is heterogeneous in individuals with asthma which might be partly caused by genetic variation in the ADRB2 gene. Various ADRB2 polymorphisms have been described and studies have shown a reduced response to regularly scheduled salbutamol in patients with the Arg/Arg genotype compared to those with the Gly/Gly genotype at position 16 of the ADRB2 [Israel *et al.* 2004, 2000; Taylor *et al.* 2000]. Similar findings were reported in some but not all studies with salmeterol [Bleecker *et al.* 2006; Wechsler *et al.* 2006; Taylor *et al.* 2000]. The question is whether or not these results can be extended to individuals using LABAs and receiving also ICS [Hall, 2006]. One study showed no pharmacogenetic effect of ADRB2 variation on therapeutic response in asthmatic patients taking LABAs in combination with ICS [Bleecker *et al.* 2007]. However, the role of ADRB2 genotype on efficacy and safety of LABAs, even in combination with ICS, in patients with asthma has to be established.

Corticosteroids

Corticosteroids, because of their multiplicity of anti-inflammatory activities, are considered the agents of choice in an inflammatory disease such as asthma. Their efficacy is proved by pathological and clinical findings. In airway biopsy specimens from patients with asthma who have had prolonged treatment with ICS, the histologic abnormalities typical of asthma have been shown to diminish [Fanta, 2009]. On the clinical ground, ICS constitute the drug class that has the greatest effect in achieving well-controlled asthma. Regular treatment with ICS reduces the frequency of symptoms and the need for rescue bronchodilators, improves the quality of life and decreases the risk of serious exacerbations for patients with asthma. In two double-blind trials, early initiation of budesonide in mild persistent asthma was associated with decreased risk of severe asthma exacerbation and better pulmonary function in comparison with placebo [O'Byrne *et al.* 2006; Pauwels *et al.* 2003]. In addition, by reducing AHR, this therapy may alter the basic property of the airways that makes them asthmatic, reducing their high sensitivity to all triggers of asthma. However, ICS suppress but do not cure asthmatic inflammation: markers of airway inflammation, such as exhaled nitric oxide concentrations, and AHR return to baseline approximately 2 weeks after the use of ICS has been stopped [Sovijarvi *et al.* 2003].

Observational data also suggest that ICS diminish hospitalizations and mortality from asthma [Suissa *et al.* 2000; Donahue *et al.* 1997]. However, evidence is lacking to indicate that long-term use of ICS can prevent the progressive decline of lung function observed in some asthmatic patients [O'Byrne *et al.* 2009; Childhood Asthma Management Program Research Group, 2000].

Not all patients with asthma are responsive to ICS therapy. Some studies suggest that up to 35% of patients may not experience improvements in FEV_1 and/or airway hyper-reactivity [Szefler *et al.* 2002]. Neutrophilic inflammation of the airways is less likely to respond than eosinophilic inflammation. In addition, patients who smoke may be relatively resistant to the initial effects of therapy with low-dose ICS [Lazarus *et al.* 2007; Tomlinson *et al.* 2005]. Finally, genetic differences may cause a nonresponsiveness to corticosteroids.

It is known that both local and systemic side effects may occur as a consequence of ICS therapy. Pharyngeal and laryngeal side effects include sore throat, weak or hoarse voice and candidiasis. A patient's risk of developing adverse systemic effects from ICS is influenced by several factors, including the dose delivered to the patient, the delivery system used, and individual differences in the patient's response to the corticosteroids. Approximately 80–90% of an inhaled dose is deposited in the oropharynx, swallowed and subsequently absorbed from the gastrointestinal tract. Drug that is absorbed from the gastrointestinal tract undergoes 'first pass metabolism' in the liver, which results in the majority of the absorbed drug being converted into inactive forms for excretion. The remainder enters the systemic circulation and contributes to systemic side effects. Ten to twenty per cent of an inhaled dose enters the lung. This fraction exerts the therapeutic effect and is then absorbed directly into the systemic circulation. Thus, the drug that is absorbed from the lung has relatively greater systemic impact compared with that absorbed through the gut because there is no 'first pass metabolism' after lung absorption. Apart from bruising, long-term adverse systemic effects are not generally observed among adults taking low-to-medium doses. At high doses (usually $>1000\,\mu g$ of beclomethasone per day or equivalent), the risks of side effects increase. The most frequent of them are adrenal

suppression, growth deceleration in children, cataracts and elevated intraocular pressure. In older adults with asthma, ICS reduce bone mineral density after long-term, high-dose therapy [Irwin and Richardson, 2006]. To minimize these side effects, strategies that can achieve asthma control without using high doses of ICS and step down treatment to the lowest possible dose of ICS that maintains symptom control are desirable [Lemanske *et al.* 2001]. In children, growth retardation is a concern but some data suggest that prepubescent school-age children who continue to receive long-term treatment with ICS ultimately reach their normal predicted height [Childhood Asthma Management Program Research Group, 2000; Agertoft and Pedersen, 2000].

Leukotriene modifiers

Leukotrienes C_4, D_4, and E_4 are potent chemical mediators of asthma. Their actions include stimulation of bronchoconstriction, mucus hypersecretion, microvascular leakage with oedema formation, eosinophil chemoattraction. Two types of medications block these effects: a 5-lipoxygenase enzyme inhibitor that blocks production of leukotrienes and LTRAs that are selective cysteinyl (Cys)-LT_1 receptor antagonists [Montuschi *et al.* 2007].

The 5-lipoxygenase inhibitor zileuton is an oral agent which has been found especially beneficial in aspirin-intolerant asthmatics [Dahlen *et al.* 1998]. The reason is that asthmatic patients with aspirin sensitivity typically make excess amounts of leukotrienes. A major side effect of zileuton is a reversible chemical hepatitis in 2–4% of patients.

Currently available oral LTRAs include zafirlukast, montelukast and pranlukast, which is on the market in Japan [Montuschi, 2008]. They are generally well tolerated and montelukast has been approved for the treatment of asthma in children as young as 6 months old. Reports of an association with Churg–Strauss syndrome in a small number of patients in whom oral corticosteroids were withdrawn in concert with initiation of LTRAs may reflect the possibility that steroid withdrawal simply unmasks the developing disease [Hauser *et al.* 2008].

Bronchodilatation occurs within hours of the first dose and levels of circulating blood eosinophils decrease in response to treatment with LTRAs [Reiss *et al.* 1998]. LTRAs improve symptoms and prevent exacerbations in some patients with moderate asthma and suboptimal control on ICS: two randomized, double-blind controlled studies have shown a beneficial effect of adding montelukast to inhaled budesonide [Price *et al.* 2003; Vaquerizo *et al.* 2003]. In a different IMPACT trial (Investigation of Montelukast as Partner Agent for Complementary Therapy), the combination of montelukast and fluticasone at a dose of 200 μg/day was equally effective as the combination salmeterol and fluticasone in reducing asthma exacerbations and nocturnal asthma and improving quality of life [Bjermer *et al.* 2003]. In another study, montelukast proved to be superior to salmeterol in combination with fluticasone in preventing exercise-induced bronchoconstriction, as montelukast was not associated with development of tolerance [Storms *et al.* 2004]. A meta-analysis reported that a combination of ICS plus LABA is more effective than LTRAs as add-on therapy to ICS [Ducharme *et al.* 2006]. However, it should be considered that many patients included in this Cochrane review were preselected as good beta-2 responders when they entered the trials, introducing a bias in the selection of asthmatic patients that could make the conclusions drawn from selected clinical trials not directly applicable to 'real life'. In addition to improving asthma control, LTRAs facilitate reduction of ICS dosage [Tamaoki *et al.* 1997]. However, LTRAs used alone are generally less effective than ICS in improving lung function and number of symptom-free days [Bleecker *et al.* 2000]. As a result, an ICS is the recommended first choice drug in patients with persistent asthma, including children, and LTRAs are an alternative treatment for mild asthma [NAEPP, 2007]. Persons with asthma who are obese or who smoke cigarettes may particularly benefit from treatment with LTRAs [Lazarus *et al.* 2007; Peters-Golden *et al.* 2006]. Anti-leukotriene agents may also be helpful in the setting of mild persistent asthma in which exercise-induced bronchospasm is a prominent feature because LTRAs have been found to inhibit exercise-induced bronchoconstriction [Edelman *et al.* 2000].

Chromones

The drugs cromolyn and nedocromil are commonly grouped together as chromones, also called cromoglycates. They are alternative choices when initiating regular controller therapy in patients with mild asthma, although ICS are

the preferred agents [GINA, 2008; NAEPP, 2007]. They can also be used in short-term prevention of bronchospasm although they have no acute bronchodilating capacity. Chromones prevent mast cell degranulation and have anti-inflammatory properties. The mechanism of action probably involves some processes that act to stabilize airway mast cells and perhaps other inflammatory cells. In this way chromones have potent effects in preventing both early and late asthmatic responses to inhaled allergens and reducing airway reactivity to inhaled irritants, such as cold air. They have clinical utility in two distinct clinical situations: prophylactic use before exposure to a known asthma trigger and chronic use as a controller therapy. As prophylactic drugs, a single treatment of inhaled cromolyn or nedocromil administered 10–15 minutes before a trigger exposure (e.g. exercise or pollen) is usually sufficient to provide protection. The combination with beta agonists is additive in benefit [Latimer *et al.* 1983]. The chromones may also be used as long-term anti-inflammatory controller agents [GINA, 2008; NAEPP, 2007; Hoag and McFadden, 1991]. A recent review examined trials comparing nedocromil with placebo in the management of chronic asthma in children [Sridhar and McKean, 2006]. Short-term trials (1–3 months) showed some improvements in lung function with nedocromil while two longer studies (6 months duration and 4–6 years duration, respectively) found variable improvement in symptom-free days and some improvement in lung function [Sridhar and McKean, 2006]. Overall, these findings suggested mild efficacy of nedocromil in chronic asthma. Moreover, other studies concluded that chromones were less effective than ICS both in terms of improvement in lung function and asthma control [Childhood Asthma Management Program Research Group, 2000; Guevara *et al.* 2006]. One study compared 1-month therapy with cromolyn with 1-month therapy with montelukast in asthmatic children [Bukstein *et al.* 2003]. Daily rescue use of salbutamol was reduced by 38% and 23% by montelukast and cromolyn, respectively, and patients were more compliant with montelukast. However, further comparative trials of longer duration are needed, as chromones require 1–3 months to reach full efficacy. Both cromolyn and nedocromil have remarkably favourable therapeutic indices and appear to have minimal systemic absorption after inhalation. They have the advantage of being virtually devoid of short-term and long-term adverse side effects.

Anti-IgE

The anti-IgE monoclonal antibody omalizumab is the first biologic immunoregolatory agent available to treat asthma. It binds to the portion of IgE that recognizes its receptor on the surface of mast cells and basophils and, when given intravenously, reduces circulating IgE levels by 95% [Fanta, 2009]. Omalizumab is a treatment option limited to patients with elevated serum levels of IgE (between 30 and 700 IU/ml) and with documented sensitization to a perennial aeroallergen. Inclusion criteria for patients with asthma enrolled in clinical trial with anti-IgE are shown in Box 1. Omalizumab is administered subcutaneously every 2 or 4 weeks and its current indication is for patients with severe allergic asthma who are uncontrolled on ICS. Treatment with omalizumab has been found to reduce the frequency of asthmatic exacerbations in patients already taking other controller medications and to decrease the ICS dose [Humbert *et al.* 2005; Busse *et al.* 2001]. Anti-IgE appears to be safe as add-on therapy but a limitation to a more widespread use derives from its high cost.

Classification of asthma and stepping up and stepping down therapy

The first step in determining the appropriate therapy for patients who are not already on a controller medication is classifying the severity of the patient's asthma (Table 1). Asthma severity is determined by considering the following factors [Humbert *et al.* 2005; Busse *et al.* 2001]: reported symptoms over the previous 2–4 weeks; current level of lung function; and number of exacerbations requiring oral corticosteroids per year. On this basis, classification of severity of asthma includes intermittent, mild persistent, moderate persistent, and severe asthma.

The GINA classification of asthma severity has some small differences from the above-reported

Box 1. Inclusion criteria for anti-IgE therapy.

Age 12 years and older
Moderate-to-severe persistent allergic asthma not adequately controlled with inhaled corticosteroids
IgE level of 30–700 IU/ml
Positive allergen skin or specific IgE tests to a perennial aeroallergen

Table 1. Classification of asthma severity before pharmacological therapy according to the National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma (GINA) guidelines.

Classification	Step	NAEPP guidelines*	GINA guidelines**
Intermittent	1	Symptoms $\leq$ 2 days/week Exacerbations 0–1/year*** Nighttime awakenings $\leq$ 2/month SABA use $\leq$ 2 days/week FEV_1 > 80% predicted FEV_1/FVC normal No interference with normal activity	Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month FEV_1 or PEF $\geq$ 80% predicted FEV_1 or PEF variability < 20%
Mild persistent	2	Symptoms > 2 days/week but not daily Exacerbations $\geq$ 2/year*** Night-time awakenings 3–4/month SABA use > 2 days/week, but not daily and not more than once on any day FEV_1 > 80% predicted FEV_1/FVC normal Minor limitations of normal activity	Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month FEV_1 or PEF $\geq$ 80% predicted FEV_1 or PEF variability < 20–30%
Moderate persistent	3	Daily symptoms Exacerbations $\geq$ 2/year*** Nighttime awakenings 1/week but not daily Daily use of SABA FEV_1 > 60% but < 80% predicted FEV_1/FVC reduced 5% Some limitations of normal activity	Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of SABA FEV_1 or PEF 60–80% predicted FEV_1 or PEF variability > 30%
Severe persistent	4–5	Symptoms daily Exacerbations $\geq$ 2/year*** Nighttime awakenings often > 7/week Use of SABA several times per day FEV_1 > 60% predicted FEV_1/FVC reduced > 5% Normal activity extremely limited	Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitations on physical activities FEV_1 or PEF $\leq$ 60% predicted FEV_1 or PEF variability > 30%

*From NAEPP Guidelines, updated 2007;
**from GINA Guidelines, updated 2008;
***exacerbations requiring oral systemic corticosteroids.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; SABA, short-acting β_2-agonist.

NAEPP classification mainly based on the peak expiratory flow (PEF) variability which must be less than 20% in intermittent asthma, is between 20% and 30% in mild persistent and more than 30% in moderate and severe persistent asthma [GINA, 2008]. It is important to recognize that asthma severity involves both the severity of the disease and its responsiveness to treatment. In this way, severity is not an unvarying feature of an individual patient's asthma but may change over time.

A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma by reducing impairment and reducing risk (Table 2). The goal for reducing impairment is to prevent chronic symptoms, to require infrequent use of SABAs for quick relief of symptoms, to maintain normal or near normal pulmonary function and normal activity levels. The goal for reducing risk is to prevent recurrent exacerbations and progressive loss of lung function [NAEPP, 2007]. A step treatment corresponds to each category of asthma severity. A patient is then assigned to one of the different steps for treatment. According to the GINA guidelines, a fifth step is also considered for more severe asthma whereas the NAEPP guidelines expand the stepwise approach to include six steps of care to simplify the actions within each step [GINA, 2008; NAEPP, 2007]. Step-down therapy is essential to identify the minimum medication necessary to maintain control.

Regular or on-demand treatment in mild persistent asthma

Current guidelines recommend daily long-term controller medications in patients with mild persistent asthma [GINA, 2008; NAEPP, 2007]. The preferred long-term controller is ICS at low-doses. Alternatively, LTRAs and chromones can be used [NAEPP, 2007]. Theophylline is not generally administered as monotherapy, but its

Table 2. Classification of asthma and stepwise therapy: simplified approach to asthma treatment according to the National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma (GINA) guidelines.

Classification	Step	NAEPP guidelines*	GINA guidelines**
Intermittent	1	As-needed SABA EIB: SABA or chromone before exercise	As-needed SABA EIB: SABA before exercise; Alternative: chromone or LTRA
Mild persistent	2	Low-dose ICS Alternative: chromone, LTRA or theophylline	Low-dose ICS Alternative: LTRA
Moderate persistent	3	Low-dose ICS plus LABA or medium-dose ICS Alternative: low-dose ICS plus either LTRA or theophylline	Low-dose ICS plus LABA Alternative: medium-dose ICS or low-dose ICS plus either LTRA or theophylline
Severe persistent	4	Medium-dose ICS plus LABA Alternative: medium-dose ICS plus either LTRA or theophylline	Medium- or high-dose ICS plus LABA Alternative: medium- or high dose ICS (plus LABA) plus either LTRA or theophylline
Severe persistent	5	High-dose ICS plus LABA Consider: omalizumab	Add: oral corticosteroid and/or omalizumab
Severe persistent	6	High-dose ICS plus LABA plus oral corticosteroid Consider: omalizumab	

*From NAEPP Guidelines, updated 2007, in subjects 12 years of age and adults;
**from GINA Guidelines, updated 2008, in children > 5 years of age, adolescents, and adults.
Abbreviations: EIB, exercise-induced bronchoconstriction; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist.

combination with a low dose of ICS can be more effective and safer than high doses of ICS in patients with moderate asthma not sufficiently controlled with ICS [Evans *et al.* 1997]. Regular use of ICS reduces the frequency of symptoms and the need for SABAs for symptom relief, improves the quality of life and decreases the risk of exacerbations. In the OPTIMA trial, patients with mild-to-moderate asthma treated with inhaled budesonide for 1 year had a reduced rate of severe exacerbations, days with asthma symptoms, and poorly controlled asthma days and nights in comparison with subjects treated with placebo [O'Byrne *et al.* 2001]. In the inhaled Steroid Treatment As Regular Therapy in early asthma (START) study, more than 7000 patients with new-onset asthma were treated with inhaled budesonide or placebo for 3 years and budesonide reduced the number of severe exacerbations and improved FEV_1 in comparison with placebo [Pauwels *et al.* 2003]. The efficacy of ICS has also been proved in infants and preschool-aged children (< 5 years of age) with recurrent wheezing or asthma, according to the results of a recently published meta-analysis [Castro-Rodriguez and Rodrigo, 2009]. The study analyzed data from 29 randomized, controlled trials comparing ICS *versus* placebo in 3592 children: patients who received ICS had significantly less wheezing/asthma exacerbations than those on placebo and this effect was independent of age, atopic condition, type of ICS used, and study duration. In addition, children treated with ICS had more clinical (change in symptom score) and functional (change in PEF and FEV_1 from baseline) improvement than those on placebo [Castro-Rodriguez and Rodrigo, 2009].

Thus, regular treatment with ICS achieves and maintains asthma control, although there is no agreement that it prevents progressive loss of lung function over time [Pauwels *et al.* 2003; Childhood Asthma Management Program Research Group, 2000]. Some studies suggest that there is an initial period during which corticosteroids can prevent airway remodelling in newly diagnosed patients with asthma, after which their effect is reduced or lost [Selroos *et al.* 1995; Haatela *et al.* 1994]. Two trials in infants and children with wheezing and risk factors for development of asthma indicate that ICS do not alter the natural history of the disease [Bisgaard *et al.* 2006; Guilbert *et al.* 2006]. However, asthma has long-term effects on lung function as indicated by the Copenhagen City Heart Study that showed greater declines in FEV_1 over time in patients with asthma compared with those observed in nonasthmatic subjects [Lange *et al.* 1998]. These asthma-related effects on lung function could be due to persistent, uncontrolled, airway inflammation.

In an animal model of human asthma, montelukast, a LTRA, prevents allergen-induced airway changes and reverses structural changes including airway smooth muscle cell layer thickening and subepithelial fibrosis, that are not affected by corticosteroid treatment [Henderson *et al.* 2006]. A reduction in basal membrane thickening [Ward *et al.* 2002] and subepithelial collagen deposition [Hoshino *et al.* 1999] has also been reported with ICS, although these effects seem to have little impact on the clinical evolution of asthma [Bisgaard *et al.* 2006]. In one biopsy study, montelukast (10 mg once daily for 8 weeks) reduced myofibroblast accumulation in the airways of patients with asthma following low-dose allergen challenge [Kelly *et al.* 2006]. However, more studies are required to determine whether LTRAs prevent airway remodelling and/or reverse established airway structural changes in patients with asthma.

It can be hypothesized that patients with mild asthma who do not perceive the need for daily therapy may be using their treatment intermittently. Three recent studies have faced this issue and have compared daily *versus* as-needed therapy for mild persistent asthma: in the Improving Asthma Control (IMPACT) study, the level of asthma control obtained with the use of intermittent treatment with budesonide was compared with that obtained with use of intermittent plus daily treatment with a controller medication, either budesonide or zafirlukast [Boushey *et al.* 2005] (Figure 2). In the Beclomethasone plus Salbutamol (BEST) study, it was investigated whether the symptom-driven use of a combination of beclomethasone and salbutamol in a single inhaler would be as effective as the regular use of inhaled beclomethasone and superior to the as-needed use of inhaled salbutamol [Papi *et al.* 2007]. Finally, in the Helsinki Early Intervention Childhood Asthma Study, the anti-asthmatic efficacy and systemic effect of daily versus as-needed budesonide in the treatment of early, mild persistent asthma in children were evaluated [Turpeinen *et al.* 2008].

The IMPACT study was a double-blind trial in which 225 adults with long-standing mild persistent asthma were randomized to receive daily treatment with inhaled budesonide (200 μg b.i.d.), oral zafirlukast (20 mg b.i.d.) or placebo for 1 year. In addition, all patients were instructed in the use of intermittent short-course corticosteroid treatment (inhaled budesonide at a dose of 800 μg b.i.d. for 10 days or oral prednisone at a dose of 0.5 mg per kilogram of body weight per day for 5 days) guided by a symptom-based action plan [Boushey *et al.* 2005]. The budesonide group had significantly greater improvements in prebronchodilator FEV_1, bronchial reactivity, sputum eosinophils, exhaled nitric oxide, and symptom-free days but no significant differences between groups were found for morning PEF from randomization to the end of the trial, the primary outcome variable, quality of life and asthma exacerbations. The authors concluded that it may be possible to treat mild persistent asthma with short, intermittent courses of inhaled or oral corticosteroids taken when symptoms worsen [Boushey *et al.* 2005]. However, it should be noted that (1) regular treatment with budesonide was superior to intermittent treatment with corticosteroids in reducing airway inflammation as reflected by decreased sputum eosinophil counts and exhaled nitric oxide concentrations; (2) regular treatment with inhaled budesonide reduced sputum eosinophil cell counts and exhaled nitric oxide concentrations; (3) even more interestingly, at the end of the study, the group of asthmatic patients that received intermittent treatment with corticosteroids had increased sputum eosinophil cell counts and exhaled nitric oxide concentrations over baseline values, indicating that airway inflammation increases if not regularly treated with ICS. Continuous treatment with inhaled budesonide also caused a significant improvement in airway hyper-reactivity that was not observed with intermittent treatment with corticosteroids or continuous treatment with zafirlukast. These data indicate that a similar degree of asthma control as assessed by symptoms and lung function tests (except prebronchodilator FEV_1) can be achieved with corticosteroids on demand and regular treatment with ICS. However, chronic treatment with ICS was superior to intermittent treatment in reducing exhaled nitric oxide concentrations and sputum eosinophil cell counts, two validated biomarkers of airway inflammation, although these were not the primary outcome variables of this trial. These effects might have important implications in the management of patients with asthma as controlling airway inflammation might prevent and/or reduce the progression of airway remodelling and, consequently, worsening of symptoms and lung function [Canonica, 2006]. The significance of clinical trials aiming at comparing intermittent *versus* regular therapy of asthma should also be interpreted by taking into account the

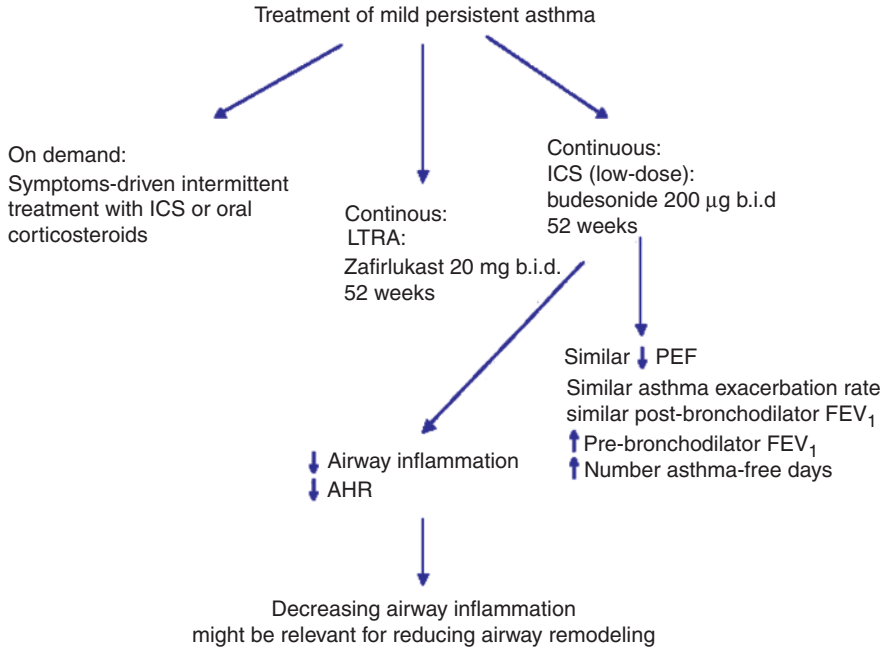

Figure 2. Main results of the Improving Asthma Control (IMPACT) study. AHR, airway hyper-responsiveness; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; PEF, peak expiratory flow.

effects of the different pharmacological strategies on airway inflammation. This emphasizes the need for searching for and validating noninvasive biomarkers of airway inflammation that should be incorporated in future clinical trials with antiasthmatic drugs.

The BEST study was a 6-month, double-blind, double-dummy, randomized, parallel-group trial in which 455 patients with mild persistent asthma were randomly assigned to receive one of the four inhaled treatments: placebo twice daily plus as-needed combination therapy (250 µg of beclomethasone and 100 µg of salbutamol in a single inhaler); placebo twice daily plus as-needed therapy (100 µg of salbutamol); regular beclomethasone therapy (250 µg twice daily) plus salbutamol (100 µg) as-needed; or regular combination therapy (250 µg of beclomethasone and 100 µg of salbutamol in a single inhaler) twice daily plus salbutamol as-needed [Papi *et al.* 2007]. The morning PEF, which was the primary outcome, during the last 2 weeks of the 6-month treatment was significantly higher and the number of exacerbations during the 6-month treatment was significantly lower in the as-needed combination therapy group than in the as-needed salbutamol therapy group, but the values in the as-needed combination therapy group were not significantly different from those in the groups receiving regular beclomethasone therapy or regular combination therapy. The authors concluded that the symptom-driven use of inhaled beclomethasone and salbutamol is as effective as regular use of inhaled beclomethasone twice daily in patients with mild asthma [Papi *et al.* 2007]. However, as no biomarker of airway inflammation was measured in this study, it is not known whether these pharmacological strategies are equivalent for controlling airway inflammation.

The Helsinki Early Intervention Childhood Asthma Study was an 18-month intervention trial in which 176 children aged 5–10 years with newly detected asthma were randomly assigned to three treatment groups: continuous budesonide (from 400 µg twice daily to 100 µg twice daily) for months 1–18; continuous budesonide for months 1–6, then budesonide for exacerbations as-needed for months 7–18; or disodium cromoglycate (DSCG) (10 mg t.d.s.) for months 1–18. Compared with DSCG the initial regular budesonide treatment resulted in a significantly improved lung function, fewer exacerbations and a small but significant decline in growth velocity. During months 7–18, patients receiving continuous budesonide treatment had significantly fewer exacerbations compared to the other groups. No significant differences between treatment groups were observed in the

morning PEF. The results of this study showed that regular use of budesonide afforded better exacerbation control but more systemic side effects than intermittent use of budesonide given as-needed [Turpeinen *et al.* 2008]. In analogy to the BEST study, the effects of the different therapeutic approaches on airway inflammation were not assessed. The three studies are not directly comparable for differences in population, study design, and medications used. The conclusions are not univocal and support the concept that different pharmacological strategies with apparently similar efficacy can be used in the treatment of mild persistent asthma.

On-demand treatment is certainly more accepted by patients with mild asthma who have infrequent symptoms because this approach helps in overcoming a possible poor compliance with a regular treatment. Moreover, considerations about the economic burden and the potential side effects of a chronic controller therapy may further contribute to favour a self-management plan of symptom-driven treatment, especially in young patients who may require life-long therapy with ICS. However, even if on-demand treatment seems to be clinically effective, it does not suppress the chronic airway inflammation or the AHR associated with asthma, as shown also in the IMPACT study [Boushey *et al.* 2005]. Thus, there is the possibility that patients without a regular treatment with ICS may develop a more severe asthma accompanied by a progressive loss of lung function [Fabbri, 2005]. However, the link between inflammation and clinical and functional outcomes is far from clear [Lazarus, 2006]. Persistent airway inflammation has been described in patients with complete clinical remission of asthma [Van den Toorn *et al.* 2001]. The clinical implications of this finding have to be clarified. Another important issue is a better understanding of which outcomes are to be chosen in clinical trials evaluating different therapeutic strategies. The morning PEF, which was the primary outcome in both the IMPACT and BEST studies, could not be a very sensitive efficacy parameter to assess the asthma control in adults, as already shown in children [Childhood Asthma Management Program Research Group, 2000; Turpeinen *et al.* 2008]. The assessment of asthma control should incorporate not only current clinical control, such as symptoms, reliever use and lung function, but also future risk, such as exacerbations and lung function decline [Taylor *et al.* 2008]. As reported above, there are conflicting data on the efficacy of a regular treatment with ICS in preventing the accelerated decline of lung function evidenced in patients with asthma [James *et al.* 2005; Pauwels *et al.* 2003; Childhood Asthma Management Program Research Group, 2000]. Both the IMPACT and BEST studies are too short to address this issue and longer randomized clinical trials are required to properly assess whether airway inflammation must be suppressed over time to prevent the progression of asthma. Until the relationship between symptoms, lung function tests, inflammatory biomarkers, and longer-term variables such as exacerbations and remodelling is better understood, the regular treatment seems to be more appropriate than on-demand therapy to warrant a greater control of asthma.

Another question is whether all patients with mild asthma should be treated with daily long-term therapy with ICS. It is likely that asthma is a more heterogeneous disease than was previously recognized and that current treatment guidelines need a fine-tuning change [Lazarus, 2006]. In clinical practice, patients with mild persistent asthma are not easy to identify, likely because many patients move up and down through the continuum represented by the severity classification. Patients with mild asthma who have their disease well controlled by regular treatment with ICS might be treated with only on-demand therapy plan as an intermediate step towards the withdrawal of controller medication [Fabbri, 2005]. These patients need a very careful assessment to avoid an underestimation of the severity of their disease and a strict follow-up to verify the efficacy of the on-demand treatment in controlling asthma. They probably represent only a select subgroup of patients with mild asthma in whom the on-demand therapy might be successfully adopted.

Conclusions

In view of the fact that airway inflammation has a central role in the pathophysiology of asthma and that long-term control of asthma is principally based on anti-inflammatory drugs, comparison of different pharmacological strategies for achieving asthma control should include assessment of airway inflammation. At present, very few clinical trials on pharmacological therapy of asthma have incorporated inflammatory outcomes partially due to the relative lack of noninvasive biomarkers of airway inflammation. Exhaled nitric oxide measurement has been approved in the clinical

setting for monitoring of pharmacological therapy in patients with asthma [Silkoff *et al.* 2004]. Although semi-invasive and less feasible in some groups of patients (e.g. children), analysis of sputum eosinophils is standardized and is a direct measure of airway inflammation [Petsky *et al.* 2007]. These techniques should be included in clinical trials with anti-asthmatic drugs. Identification and validation of new non-invasive techniques and biomarkers for assessing airway inflammation is essential for a better understanding of the airway inflammatory process that characterizes asthma. Persistent airway inflammation might lead to airway remodelling with onset or worsening of symptoms, deterioration in lung function, and reduced response to pharmacological therapy. However, the relationships between chronic airway inflammation and airway remodelling need to be clarified. The relative short duration of asthma clinical trials makes it difficult to establish the effect of uncontrolled airway inflammation on progression of asthma and disease severity. Longer clinical trials that incorporate biomarkers of airway inflammation are required to address this issue.

In summary, choosing the 'right' pharmacological strategy (regular *versus* on-demand treatment) for asthma control is currently difficult due to the fact that (1) inflammatory outcome measures have generally not been incorporated in asthma clinical trials; (2) the relationships between chronic airway inflammation and airway remodelling are largely unknown; (3) current clinical asthma trials that are generally based on symptomatic and functional outcome measures are too short to assess the impact of regular anti-inflammatory therapy on natural history of asthma; (4) asthma is a heterogeneous disease and different phenotypes of asthma patients likely requiring a different therapeutic approach can be identified, even in the same class of asthma severity.

Although the IMPACT and BEST studies suggest that on-demand therapy in some patients with mild persistent asthma achieves a similar degree of asthma control based on symptoms and functional outcomes, the IMPACT study indicates that regular and on-demand therapy is not equivalent for controlling airway inflammation. Moreover, in children with mild persistent asthma, the Helsinki study indicates that regular treatment with ICS significantly reduces the rate of exacerbations of asthma, a primary objective for asthma control, compared with on-demand therapy. At present, there are not sufficient data to change the recommendations of the current guidelines for a regular therapy with low-dose ICS in the majority of patients with mild persistent asthma. In patients with intermittent asthma with evidence for elevated airway inflammation (e.g. exhaled nitric oxide, sputum eosinophils), the decision of starting a regular anti-inflammatory therapy is still controversial due to the inadequate knowledge of the long-term consequences of uncontrolled airway inflammation on airway structure, lung function and risk of acute asthma exacerbation. On-demand treatment with SABAs as suggested by the international guidelines is a reasonable option. Alternatively, courses of anti-inflammatory drugs for asthma (e.g. low-dose ICS, LTRAs) can be prescribed to subgroups of patients with intermittent asthma including those with seasonal allergic asthma or perennial allergic asthma exposed to triggering factors (e.g. cold, upper respiratory tract infections) also considering the good tolerability of these drugs. However, patients with intermittent asthma should be closely monitored to identify the time at which starting pharmacological therapy is required.

Guidelines for asthma management are a valuable tool, although they are necessarily based on a strategy directed to the best outcome in a group of patients. Asthma phenotyping is becoming central for asthma management. The issue of regular *versus* on-demand treatment of intermittent and mild persistent asthma would be better addressed if considered within an individualized approach to asthma management and assessment. Identification of clinical, functional, morphological and biochemical phenotypes of patients with asthma and its clinical implications is likely to lead to a tailored, individualized, pharmacological therapy and asthma management.

Conflict of interest statement

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