

Symptom-Based Controller Therapy: A New Paradigm for Asthma Management

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Abstract Appropriate management of persistent asthma, according to US and international guidelines, requires daily use of controller medications, most generally, inhaled corticosteroids (ICS). This approach, although effective and well established, imposes burdens of treatment and side effects onto asthma patients. A growing body of evidence suggests that patients with persistent asthma need not be managed with daily ICS, but rather can use them on an intermittent basis, occasioned by the occurrence of symptoms sufficient to warrant treatment with a rescue inhaler. Large, randomized, controlled studies, over a range of asthma severity, and in a range of ages from pediatrics to adults, suggest that, in well-selected patients, a symptom-based approach to administering controller therapy may produce equivalent outcomes, while reducing exposure to ICS. The concept of providing anti-inflammatory treatment to the patient, at the time inflammation is developing, is termed ‘temporal personalization’. The evidence to date suggests that symptom-based controller therapy is broadly useful in selected asthma patients, and is a management approach that could be incorporated into US and international guidelines for asthma.

Keywords Asthma · Inhaled corticosteroids · Symptom-based controller therapy · Management · Treatment

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Abbreviations

ACRN	US Asthma Clinical Research Network
BASALT	Best Adjustment Strategy for Asthma in the Long Term
BEST	Beclomethasone plus Salbutamol Treatment
ICS	Inhaled corticosteroids
IMPACT	Improving Asthma Control
MIST	Maintenance vs. Intermittent inhaled Steroids in wheezing Toddlers
NHLBI	US National Heart Lung and Blood Institute
NO	Nitric oxide
TREXA	Treating children to prevent Exacerbations

Introduction

Asthma is a heterogeneous disorder characterized by airway inflammation, airway hyperresponsiveness, and variable air-flow limitation [1]. Current guidelines for the management of asthma recommend controller therapies based on the frequency and occurrence of daytime and nighttime symptoms, the frequency of use of short-acting beta₂-agonists for relief of symptoms, the frequency and occurrence of clinically important worsening of asthma (exacerbations, mild and severe), the presence and severity of pulmonary function embarrassment, and other factors based on the clinical judgment of the physician. From these considerations, a severity assessment is made: intermittent versus persistent asthma. For patients with persistent asthma, additional discrimination of the level of severity (Step 2 through 5 in the US NHLBI Guidelines [1]) is made which then informs the intensity and types of controller therapy. Several comparable guidelines exist globally, and although there are some important differences in the details, the overall approaches recommended by the guidelines are remarkably consistent: short-acting beta₂ agonists for relief of

symptoms, and daily maintenance controller therapies (most usually inhaled corticosteroids, ICS) for all grades of persistent asthma. The guidelines are scholarly, evidence-based, and authoritative, and define an acceptable approach for diagnosing and managing asthma. They are, however, voluminous, difficult to implement, and implicitly suggest that a standardized approach will be effective for all patients. In fact, guidelines are only a first step to approaching a goal of personalized medicine, in which therapy is tailored to individual patients to maximize efficacy, and minimize toxicity and burden of treatment, in accordance with the heterogeneity of asthma.

Emerging evidence over the past decade suggests that other management approaches may provide some advantages to selected patients with asthma, particularly with respect to the question of adjustment of ICS dosing. Several strategies for adjusting ICS have been advanced, including the use of measures of airway responsiveness [2, 3], sputum eosinophil quantification [4], exhaled nitric oxide (NO) [5]. These approaches are reviewed briefly below. Each of these approaches, however, requires contact with a physician, specialized equipment, highly trained personnel, and additional expense. An alternative approach is to base the frequency of administration of ICS on the occurrence of symptoms of asthma, i.e., symptom-based controller therapy. Considerable information derived from well-controlled, large, randomized clinical trials, conducted by consortia of investigators with expertise in asthma, has accumulated to suggest that symptom-based controller therapy in selected patients with asthma is as effective as other approaches, and provides some unique advantages for asthma management, including ‘temporal personalization’ – providing the right medication (ICS) at the right time.

Clinical Studies of Symptom-Based Controller Therapy

Well-designed clinical trials have outlined the situations in which symptom-based controller therapy may be beneficial for patients. In this section, we formally review the studies, and synthesize information derived from these publications (Table 1). Although a few earlier studies, in retrospect, support the concept of symptom-based controller therapy, the first to address the question directly was the IMPACT study, conducted by the US Asthma Clinical Research Network (ACRN).

IMPACT

The subjects included in the Improving asthma control trial (IMPACT) were adults with physician diagnosed and clinically confirmed mild persistent asthma [6]. The study was double blinded, randomized, with three parallel treatments lasting for a year, to test the hypothesis that symptom-based intermittent treatment of mild asthma would be an acceptable alternative to

daily therapy. The groups were divided into group 1: daily budesonide (daily inhaled corticosteroid controller), group 2: daily zafirlukast, and group 3: daily placebo controls. All three groups were given a symptom-based action plan that included intermittent ICS, oral corticosteroids, and rescue therapy. The primary outcome in the study, change in morning peak expiratory flows in the last 2 weeks at the conclusion of the study, did not differ in the 3 groups, and no important differences in objective measures of lung function were observed. Small differences in the percentage of eosinophils in sputum, exhaled nitric oxide values, and PC20 were seen, favoring subjects treated with daily budesonide compared to treatment with oral zafirlukast or placebo. Asthma-related quality of life assessment was similar in all the groups, but the daily budesonide group also reported better scores on the asthma control score and symptom free days, as compared to intermittent group. Collectively, these data suggested that, in selected patients with mild persistent asthma, daily ICS therapy provided only small, secondary, advantages.

BEST

The subjects included in this beclomethasone plus salbutamol (albuterol) treatment (BEST) study were adults with physician-diagnosed and objective evidence of asthma [7]. The experimental design was a double-blind, double-dummy, randomized, four-group, parallel, drug-controlled trial lasting for the duration of 6 months, to test the hypothesis that symptom-based therapy with inhaled corticosteroid therapy combined with a short-acting beta2-agonist was as effective as daily controller therapy. The recruited subjects were divided into 4 groups: (1) daily beclomethasone as controller and albuterol as rescue (standard therapy), (2) combination of beclomethasone and albuterol as rescue inhaler when required, (3) albuterol for rescue only without controller, and (4) daily combination of albuterol and beclomethasone for control, and albuterol for rescue. The primary outcome of comparison between the groups was the mean rate of morning peak expiratory flow during the last 2 weeks of the study duration. Other outcomes measured in addition to more variables of PEF were: degree of asthma control, asthma symptom score in last 2 weeks, number of exacerbations, and time to first exacerbation. Additional outcomes are summarized in Table 2. As needed combination was found to be as good as daily controller therapy in outcome measures of morning PEF at the end of 6 months, FEV1, FVC, and nocturnal awakenings. All regimens with controller therapy included were found to outperform the placebo group (group 3). Small differences were seen amongst variables such as night-time PEF, daytime asthma symptoms score, night-time asthma score when compared to the control albuterol-only group. Intermittent albuterol plus beclomethasone resulted in comparable outcomes to daily budesonide,

Table 1 Overview of trials addressing intermittent/symptom-based controller therapy

Acronym	BASALT	MIST	TREXA	BEST	IMPACT
Title of trial	Best Adjustment Strategy for Asthma in the Long Term	Maintenance vs. Intermittent Inhaled Steroids in Wheezing Toddlers	Treating children to prevent Exacerbations of Asthma	Beclomethasone plus Salbutamol (albuterol) Treatment	Improving Asthma Control Trial
Year	2012	2011	2011	2007	2005
Study population	Adults	Children	Children and adolescents	Adults	Adults
Age (years)	18–65	1–4.4	6–18	18–65	18–65
Asthma severity	Mild to moderate persistent asthma	Recurrent wheezing and positive values on asthma predictive index (API) score	Mild persistent	Mild persistent	Mild persistent
Total number of subjects completing study	342	213	843	393	199
Duration of study	36 weeks (9 months)	2 weeks run-in plus 52 weeks	44 weeks (11 months)	24 weeks (6 months)	54 weeks
Number of study groups	3	2	4	4	3
Interventions	1. C = daily beclomethasone + placebo, R = albuterol + placebo (Physician assessment-based adjustment) 2. C = daily beclomethasone + placebo, R = albuterol + placebo (Biomarker based adjustment) 3. C = daily placebo + placebo, R = beclomethasone + albuterol (symptom-based adjustment)	1. C = daily budesonide (low dose), R = albuterol + placebo in AM and low-dose budesonide in PM. 2. C = daily placebo, R = albuterol + high-dose budesonide BID for 7 days during exacerbations	1. C = daily beclomethasone, R = beclomethasone + albuterol 2. C = daily beclomethasone and placebo, R = albuterol 3. C = daily placebo, R = beclomethasone + albuterol 4. C = daily placebo, R = albuterol	1. C = daily beclomethasone + albuterol, R = albuterol 2. C = daily beclomethasone, R = beclomethasone + albuterol 3. C = daily placebo, R = albuterol 4. C = daily placebo, R = beclomethasone + albuterol	1. C = daily oral placebo and inhaled beclomethasone, R = budesonide or prednisone, as needed 2. C = daily oral zafirlukast and inhaled placebo, R = budesonide or prednisone, as needed 3. C = daily oral and inhaled placebo, R = budesonide or prednisone, as needed
Primary outcome measure	Time to treatment failure	Frequency of exacerbations	Time to first exacerbation that required oral corticosteroids	Mean rate of morning peak expiratory flow in the last 2 weeks of study	Change in morning PEF from beginning to the conclusion of study
Primary result	No significant differences in time to treatment failure between groups	Comparable outcomes between daily and intermittent groups	No significant difference vs. placebo in rescue beclomethasone group	Significantly higher and comparable to daily controller therapy	No significant difference between 3 groups
Notable secondary outcome(s)	1. Asthma exacerbation rates 2. Missed days of school or work 3. Cumulative corticosteroid usage	1. Distribution of type of symptoms 2. Episode-free days 3. Frequency and distribution of respiratory viruses in nasal secretions 4. Exposure to budesonide	1. Linear growth in children 2. Frequency of treatment failures 3. Frequency of exacerbations	1. Asthma symptom scores 2. Number and severity of exacerbations	1. Symptom-free days 2. Symptom-related discomfort or impairment
Secondary results	1. Asthma exacerbation rates did not differ amongst treatment groups 2. Symptom-based adjustment group had almost half of the cumulative steroid usage as other groups. 3. Missed school or work was significantly less in symptom-based adjustment group	1. Similar distribution of symptoms 2. Similar episode-free days 3. No difference in respiratory viral isolates 4. Significantly less corticosteroid used in intermittent group	1. Less depression of linear bone growth in children using rescue beclomethasone vs. daily steroid 2. Frequency of treatment failure achieved significance as compared to control 3. Similar frequency of exacerbation vs. daily steroid	1. Compared to baseline values, % of symptom-free days in all groups except those receiving as needed albuterol. 2. % of patients with at least one exacerbation was lower in both as needed combination and regular ICS therapy.	Improvement in asthma symptom score and symptom-free days greater in budesonide treatment than with either zafirlukast or intermittent treatment
Conclusions	Among adults with mild to moderate persistent asthma symptoms based adjustment therapy was not superior to biomarker based or physician adjustment-based strategy.	In children with low impairment from asthma and frequent exacerbations requiring corticosteroids, daily low dose budesonide was not superior to intermittent high-dose regimen	ICS used as rescue with SABA show benefits over rescue SABA alone and avoids the side effect on growth associated with daily ICS therapy.	As needed treatments with combination of ICS and SABA, as well as regular treatment with ICS were superior to as needed treatment with SABA alone	In mild asthmatics on symptom based action plan, regularly scheduled treatment with daily ICS or zafirlukast had no effect on rate of severe exacerbations

C Controller therapy, R rescue therapy, ICS Inhaled corticosteroid, SABA short-acting beta agonist

Table 2 Summary of findings of BEST trial

	Comparator group: Albuterol rescue-only control group	Outcomes favoring: Controller + rescue as needed Grp 1 - daily beclomethasone Grp 2 – beclomethasone plus albuterol as rescue
Significant differences	Morning PEF	Both comparable and achieved significance
	Evening PEF	Daily controller regimen achieved significance
	Rescue medication use	Daily controller regimen achieved significance
	FEV1	As needed regimen achieved significance
	FVC	As needed regimen achieved significance
	Nocturnal awakenings	As needed regimen achieved significance
	Symptom-free days	Daily controller regimen achieved significance
No significant differences	PEF variability	Neither regimens achieved significance
	Night asthma symptoms	Neither regimens significantly different
	Daytime asthma symptoms	Neither regimens significantly different

providing some initial evidence that outcomes with regular daily treatment could be matched by intermittent therapy.

TREXA

The subjects included for the treating children to prevent exacerbations of asthma (TREXA) study were children between 5 and 18 years of age, with physician-diagnosed mild persistent asthma [8•]. The goal of this study was twofold: (1) to assess the risk or exacerbation for those children diagnosed with mild persistent asthma, who were well controlled but not using daily ICS, and (2) to assess the value of using intermittent controller (ICS) plus albuterol, triggered by symptoms and used as rescue, was effective in mitigating exacerbations. The hazard ratio for asthma exacerbations was lower in patients using albuterol plus beclomethasone on a symptom-driven basis, compared to placebo-treated patients, but the difference did not achieve statistical significance. In contrast to using daily-inhaled corticosteroid, the beclomethasone/albuterol rescue group had less protection against exacerbations. The authors of this study suggested that rescue beclomethasone can lower risk of asthma exacerbations, but its effect was less than daily ICS. However, there was a significant tradeoff between a reduced reduction in risk between daily controller and symptom-based rescue controller therapy based on the total cumulative dose inhaled. In this study, the daily controller groups were using approximately 2–2.2 puffs per day of beclomethasone, as opposed to 0.3–0.5 puffs per day in the rescue controller group, and this decreased use of ICS was reflected in the comparison of linear growth in children during the study. Using growth in height as one of the surrogates for side effects of long-term corticosteroid exposure, the investigators found that children on daily-inhaled corticosteroids had approximately 1 cm less growth as compared to

placebo group. Children using inhaled corticosteroids as rescue had comparable heights to the placebo-treated children. Accordingly, the risk (growth suppression) and benefits (reduced exacerbation) would point towards different ICS approaches; therefore, clinicians must select among these options on the basis of factors most important to individual patients and their families.

MIST

The study population for the Maintenance versus Intermittent Inhaled Steroids in Wheezing Toddlers (MIST) included children between 12 and 53 months of age who were selected based on the number of wheezing episodes in the previous year, a modified asthma predictive index, and frequency of asthma exacerbations requiring medical intervention [9•]. These children accordingly were at higher risk for exacerbations during viral infections. The study was a multicenter, double-blind, placebo-controlled, parallel group trial extending for a period of 52 weeks to test the hypothesis that a daily low-dose regimen of budesonide would be superior to an intermittent high-dose inhaled corticosteroids during episodes of pre-defined respiratory tract illness in these children. The primary outcome measure was the frequency of asthma exacerbations defined as the number of courses of oral systemic corticosteroids initiated by physician for acute wheezing. Subjects were randomized to two groups (total $n=213$) and there was no difference in primary outcome of frequency of exacerbations. These data, although not specifically applicable to asthma (particularly not to asthma in adults), do suggest that ‘temporal personalization’, or providing controller medication at the time of symptoms, is a broadly effective approach to providing control of the allergic airway inflammation that underlies bronchospasm and wheezing.

BASALT

BASALT was designed to extend the seminal findings of the IMPACT trial to adult patients with more severe asthma than was studied in IMPACT [10••]. At the same time, there was an opportunity to evaluate the utility of a novel biomarker of airway inflammation, exhaled NO. Subjects were adults with physician-diagnosed mild to moderate persistent asthma and demonstrated objective evidence of reversible airflow obstruction or positive airway hyperresponsiveness on bronchoprovocation with methacholine. The study was a multiply blinded placebo-controlled parallel 3-group trial with intervention duration of 9 months to test the hypothesis that adjustment of inhaled corticosteroids based on symptoms, or based on exhaled NO, would be superior to physician-based adjustment of asthma medications. Subjects were randomized to 3 similar groups (total $n=342$) in which adjustment of daily ICS use was based on (1) physician assessment of lung function, symptoms, and rescue albuterol use (guideline-based adjustment), (2) exhaled NO (biomarker-based adjustment), and (3) no routine daily ICS, but 2 puffs of beclomethasone was provided every time that the patient experienced symptoms that warranted the use of 2 puffs of rescue albuterol (symptom-based adjustment). The primary outcome was time to first treatment failure, which was defined by objective clinical data (peak expiratory flow rates, spirometric analyses, and increased symptoms), subjective patient data (satisfaction with symptom control, physician judgment for safety) or qualitative control (increased use of rescue inhaler above baseline, oral corticosteroids, additional asthma therapy). No differences among the three treatment strategies were seen for the primary outcome of time to first treatment failure. Despite good a priori statistical power, these three approaches to ICS adjustment were indistinguishable. In addition, no difference in treatment failure rates, asthma exacerbation rates, and proportion of treatment failures progressing to exacerbations were identified among the three groups. Moreover, several secondary outcomes favored the symptom-based adjustment approach: (1) missed days of school or work were fewer in the symptom-based group, (2) cumulative ICS dose over the duration of the trial was 50 % less in the symptom-based group, and (3) the seasonal increase in exacerbations that occurred in the Autumn season was abrogated in the symptom-based group. This benefit may have accrued because of the ‘temporal personalization’ of therapy in the symptom-based group. As triggers of asthma increase in fall, and use of the rescue inhaler increased as a result of increased symptoms, the dosing of ICS *also* increased at the time that airway inflammation would presumably be developing. Of note, use of exhaled NO during routine office visits to adjust ICS dose had no distinguishing value. The conclusion from this study was that symptom-based adjustment of therapy was equivalent to the current standard of physician assessment-based adjustment of asthma medications

in mild to moderate asthmatics. This concept of symptom-based adjustment of controller medication is appealing, as it empowers the patient to make day-to-day adjustments based on their perception of asthma symptom control, and provides important secondary benefits to patients with asthma.

Other Management Approaches

A seminal study by Sont and colleagues [2] demonstrated that, compared to asthma patients who were managed by British Thoracic Society guidelines alone, adding information from methacholine challenge testing resulted in improved lung function over the course of a year. A consequence of adding methacholine to the decision-making process for ICS dosing was that patients in the hyperresponsiveness arm received considerably more ICS than those in the routine guideline arm.

Smith and colleagues [5] studied the value of exhaled NO in asthma management in patients with persistent asthma. In a randomized, single-blind study, they demonstrated that use of exhaled NO as an adjustment metric resulted in a reduced dose of ICS over the trial, with no differences in asthma-specific outcomes. There were important differences in the implementation of dosing adjustments between BASALT and the Smith study, which likely account for the somewhat different interpretation of the value of exhaled NO in asthma management. For example, the eNO decision-points were different between the two studies.

Finally, Green and colleagues [4] conducted an innovative study of the added value of sputum eosinophils in asthma management. Patients were managed by British Thoracic Society Guidelines, with or without use of sputum eosinophil measurements. In those patients randomized to steroid adjustment based on sputum eosinophils, in addition to BTS guidelines, the mean sputum eosinophil count was significantly less, and significantly fewer exacerbations and hospitalizations were observed than in the BTS-alone control group. The total oral and inhaled steroid doses did not differ between groups. These data suggest that ‘temporal personalization’ of treatment (in this case, when sputum eosinophils rose), was an effective management strategy in asthma, although that concept was not advanced in Green’s work. Implementing consistent, accurate, and reliable sputum eosinophil counts in routine clinical settings has, however, heretofore been a significant obstacle precluding the widespread adoption of this technique.

Advantages and Limitations of Symptom-Based Controller Therapy

Taken together, these large, randomized, controlled studies suggest that symptom-based controller therapy has several

important advantages for patients with asthma. First, this approach empowers patients to take control of their disease, and this aspect may result in improved adherence to therapy. In addition, this approach is more aligned with the ‘headache’ model of treatment, in which medications are used to ameliorate symptoms, whereas heretofore the asthma community has used the ‘hypertension’ model, in which treatment persists independent of ongoing symptoms. We note here that compliance is known to be problematic in the regular treatment of hypertension in the absence of sensible symptoms, a situation analogous to regular treatment of asthma when no respiratory symptoms are present. Conversely, headaches tend to provoke desire for immediate therapy that can provide immediate relief, which would be similar to immediate treatment of breathing difficulties. In essence, the asthma patient, while still under a physician’s care, is able to form his or her own compliance routine, based on the presence or absence of symptoms, in a way that limits medication use to only that necessary.

A second consistent benefit is reduced burden of ICS. In adults, one might expect that the reduced ICS utilization could be associated with reduced medication expenditures, but that supposition has not been formally tested. In children, this reduced burden is manifest as preservation of linear growth. Achieving comparable control of asthma, while not impacting bone growth, seems to be a positive consequence of symptom-based controller approaches, especially in children.

A third benefit of this strategy, as suggested above, is that anti-inflammatory treatment is provided at the time that symptoms occur, a time when airway inflammation has been triggered. This concept of ‘temporal personalization’ has been shown to be useful in the BASALT study [10], in which the fall seasonal exacerbations were significantly blunted, and also in the Green study [4], in which treatment of high sputum eosinophils with increased ICS was associated with reduced exacerbations and hospitalizations.

The approach of symptom-based therapy is certainly not for all patients with asthma. Most studies have enrolled patients at the milder end of the asthma severity spectrum, and hence symptom-based controller approaches cannot be recommended for patients with high–moderate, or severe disease. The studies to date have not been powered to evaluate clinically important subgroups, so it is not known whether Latinos, African-Americans, or other definable groups might differentially respond to symptom-based controller therapy. Finally, symptom-based controller approaches demand that the patient be engaged with the management of his or her disease. They must commit to using an inhaled steroid *every* time that the rescue albuterol is used. They must have sufficient perception of symptoms; that is, ‘poor perceivers’ may not be good candidates for symptom-based controller therapy.

Conclusions

Considerable evidence has been developed over the past decade to suggest that daily controller therapy for asthma of mild–moderate severity may not always be necessary. In well-selected, motivated patients, comparable asthma outcomes can be achieved with reduced exposure to, and expense of, inhaled steroids. The approach empowers patients to appropriate self-management. Thus, we believe that it is time to consider adding symptom-based controller therapy to our guideline documents, to provide another management option for our patients with asthma.

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Compliance with Ethics Guidelines

Conflict of Interest Rohit Divekar, Bill T. Ameredes, and William J. Calhoun declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent With regard to the author’s research cited in this paper, all institutional and national guidelines for the care and use of laboratory animals were followed. In addition, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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