

INVITED REVIEW

The clinical impact of single inhaler therapy in asthma

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Clinical & Experimental Allergy

Summary

Background Low-dose budesonide/formoterol combination used in the SMART fashion with symptom-reactive supplemental dosing has been reported to reduce asthma exacerbations as compared to the use of budesonide alone or to lower doses of budesonide/formoterol without supplemental dosing.

Objective We undertook to review the non-exacerbation outcomes of SMART therapy and to assess the patient education implications of this treatment strategy.

Materials & Methods Systematic review.

Results Patients treated with this strategy appear to be under-treated in that the majority fail to achieve guideline-defined control standards. The SMART strategy has not been tested against equivalent or higher doses of budesonide/formoterol given in symptom-prevention fashion. Existing educational strategies that focus on recognition of poor disease control may not be applicable with SMART therapy and the use of action plans has not been clarified with this symptom-reactive strategy. There is some evidence from that the current clinical use of SMART therapy may be contaminated frequently by the concurrent prescription of short-acting bronchodilators. There is no information on long-term outcomes with a symptom-reactive ICS/LABA strategy but the use of the strategy for one year has been associated with rising sputum and airway biopsy eosinophil counts.

Conclusion Despite fewer severe exacerbations with SMART therapy as compared to ICS monotherapy or lower dose ICS/LABA therapy, the strategy produces poor day-to-day control of symptoms and is associated with increasing inflammation.

Clinical Relevance The symptom-reactive strategy described as SMART therapy is associated with poor symptom control of asthma.

Keywords asthma, budesonide, control, formoterol, inhaled corticosteroid, long-acting beta₂ agonist

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Introduction

Asthma treatment strategies that are symptom-preventive rather than symptom-reactive followed inevitably from the observation that airway instability and exacerbations were largely the consequence of unchecked airways inflammation. In pharmacologic terms, this meant earlier treatment with inhaled corticosteroids (ICS) and a diminishing role for bronchodilators [1]. In many nations, this approach has been accompanied by striking decreases in asthma mortality and morbidity despite rising asthma prevalence [2]. The expectation that earlier and better anti-inflammatory treatment would prevent airway remodelling remains an unproven hypothesis, although some studies suggest that

improved disease control blunts the pathologic changes seen over time when asthma is poorly controlled [3, 4].

Asthma management guidelines now titrate therapy based on control outcomes, rather than estimated asthma severity, severity being a parameter best evaluated *post hoc* and quantified by the least amount of maintenance medication needed to maintain control [5]. Modern guidelines have recognized the foundation role of ICS for persistent asthma, but have also noted limits to the effectiveness of ICS. If disease control is not achieved with a low to moderate dose of ICS maintenance monotherapy, greater benefit is achieved by the addition of an adjunctive agent such as a long-acting beta₂ agonist (LABA) than with further increases in the dose of ICS [6]. Such ICS/LABA combination therapy is more likely to

achieve disease control in uncontrolled asthma patients when compared with ICS monotherapy, and such results are likely to be achieved earlier and with less ICS using the combination when compared with the monotherapy approach [7–9]. Combination maintenance therapy has typically been prescribed as a constant daily dosage of ICS/LABA with a separate quick-acting bronchodilator used as needed for occasional symptom relief. More recently, international guidelines and regulatory authorities have recognized that when patients use ICS/LABA formulations containing formoterol (a quick onset, long-acting β_2 agonist), the maintenance inhaler could also be used for occasional quick relief purposes. This strategy, implemented with combination budesonide/formoterol inhalers, has become widely known as SMART (for single maintenance and reliever therapy) or SIT (single inhaler therapy) of asthma. Initially, regarded as a mere convenience or option for patients, this symptom-reactive strategy was recommended by some as having advantages over the more typical symptom-preventive strategy of constant ICS/LABA dosing with separate quick relief inhaler.

In this review, we critically examine evidence from randomized control trials of SMART therapy to translate clinical trial findings into clinical practice realities, particularly as applied to control outcomes seen and implications for patient monitoring, education and the development of action plans.

Clinical trials of SMART therapy

Limitations and caveats

The clinical trials of SMART therapy have been appraised critically and have been the subject of two Cochrane reviews [10–12]. Such reviews raise several caveats and study limitations that must be highlighted when considering this treatment strategy. First, in contrast to most contemporary asthma research and stated guideline treatment goals, the SMART trials do not use a comprehensive index of asthma control as the primary outcome variable, but with one exception have used time to first severe exacerbation as the primary outcome variable. Indeed, the reporting of conventional control outcomes as secondary outcome variables has usually been incomplete. This seems to be a lowering of the bar to earlier asthma treatment standards whereby day-to-day asthma morbidity was overlooked [13, 14]. Second, several studies have attempted to compare budesonide/formoterol combination inhalers used in SMART fashion with fluticasone/salmeterol combination inhalers used in conventional fashion [15, 16]. These studies appear to be commercially driven, and their outcomes are difficult to interpret for reasons of inadequate blinding. Given that the active inhalers

used by patients contain bronchodilators, the randomly assigned treatments cannot be blinded even when double-dummy techniques are used. Also, the comparison of these two different combinations has occasionally been confounded by the use of different delivery systems, comparing simple to use dry powder delivery inhalers to more challenging pressurized aerosol inhalers [15]. Occasionally, dosage comparisons have been suspect with doses of ICS calculated as ex-actuator for one device and nominal for another. Third, several studies have attempted to compare SMART therapy with conventional best practice with negative results [17–19]. One such study was published with emphasis on secondary outcomes, whereas the remaining negative studies remain unpublished. In these studies, conventional best practice remained undefined, suggesting that a novel intervention was compared without an adequate control intervention. Finally, the SMART strategy focuses on the timing of medication delivery with doses of inhaler used both on a scheduled basis and on an as-needed basis, and still, no study has employed available electronic dose monitoring to track inhaler usage.

Lessons from the trials

One consistent conclusion of the SMART trials is the finding that ICS/LABA is more effective at reducing exacerbations than ICS alone. O'Byrne and colleagues, for example, reported a 45% reduction in exacerbations when comparing budesonide/formoterol (100/6) one puff twice daily and the same combination as a reliever (SMART therapy) to budesonide 400 mcg twice daily with terbutaline as a reliever [20]. Similarly, Schicchitano found prolonged time to first exacerbation when comparing budesonide/formoterol (200/6) as maintenance (one puff twice daily) and as relief medication with budesonide 400 mcg twice daily with terbutaline 500 mcg/puff on as-needed basis [21]. Rabe and colleagues reported fewer severe asthma exacerbations amongst patients treated with budesonide/formoterol 100/6, one puff twice daily plus as needed (SMART therapy), when compared with patients treated with budesonide 200 mcg twice daily with terbutaline as a separate reliever [22]. (The unconventional definition of severe exacerbation in this study was expanded to include events that did not provoke symptoms in patients, but were defined by peak flow changes alone). As consistent as these findings are, they are not novel. As noted above, the superiority of ICS/LABA combinations to ICS alone has been known for almost two decades and has long been assimilated into clinical guidelines and routine practice. The finding is not specific to ICS/LABA given in SMART or SIT fashion and was equally present in earlier studies when

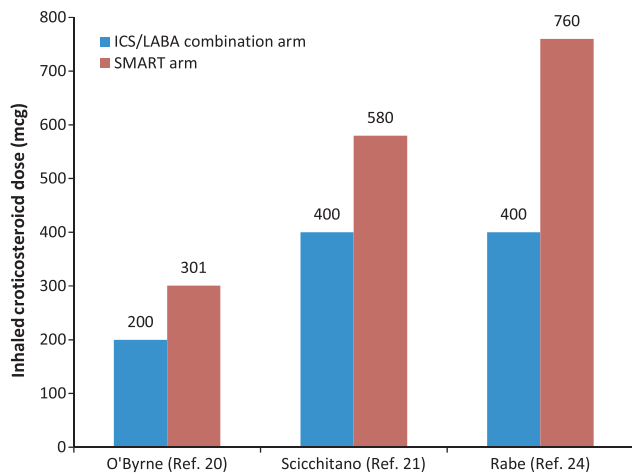


Fig. 1. Comparison of inhaled corticosteroid doses between the conventional, fixed-dose combination ICS/LABA therapy and the SMART-treated patients. On average, the SMART arm-treated patients used 50% more inhaled corticosteroid when compared with the conventional arm. (Corticosteroid doses present on top of columns).

ICS/LABA was used solely as a maintenance therapy [6, 8, 23].

The studies have also consistently shown that budesonide/formoterol given in SMART fashion is superior to budesonide/formoterol given as maintenance therapy alone, but the finding is always confounded by the inevitable dose inequality; by virtue of the freedom to take extra doses of budesonide/formoterol, patients treated with SMART strategies receive doses of ICS approximately 50% higher than comparator arms (Fig. 1). For example, Rabe and colleagues reported that SMART-treated patients using budesonide/formoterol (200/6) twice daily plus *ad lib* doses had significantly longer times to first exacerbation than patients taking budesonide/formoterol (200/6) twice daily with either terbutaline or formoterol reliever [24]. The need for reliever averaged to about one puff per day in the SMART-treated patients, so that they typically received about 200 mcg more budesonide per day than either comparator arm, an approximately 50% increase in anti-inflammatory treatment. It is also noteworthy that these poorly controlled asthma patients were deliberately destabilized at recruitment by giving less maintenance ICS during run-in than what the patients had been taking at the time of their recruitment. A more interesting comparator arm might have been a cohort of patients randomized to take a higher regular maintenance dose of budesonide/formoterol.

Having analysed the foregoing studies, Cochrane Database Systematic reviews concluded: 'Single inhaler therapy can reduce the risk of asthma exacerbations needing oral corticosteroids in comparison with fixed-dose maintenance inhaled corticosteroids. Guidelines and current best practice suggest the addition of regular

long-acting beta₂-agonist to inhaled corticosteroids for uncontrolled asthma, and single inhaler therapy has not been demonstrated to significantly reduce exacerbations in comparison with current best practice' [11].

Asthma control consequences of SMART

Our ability to prevent most asthma symptoms with effective anti-inflammatory therapy has shifted our goals for asthma treatment from rapid treatment of unstable disease to adequate asthma symptom control with unimpaired quality of life. Expected asthma control, as per internationally recognized asthma management guidelines calls for daily control with few or no daytime symptoms, no night-time symptoms, rare use of bronchodilators, no impact on day-to-day routine or work commitment with few or no acute exacerbations [25].

SMART studies have not been reported asthma control using a composite index of symptom variables to categorize patients as having achieved adequate control, but have reported some individual symptom control parameters selectively. A recent American Thoracic Society (ATS)/European Respiratory Society (ERS) statement recommends that composite index of multiple variables be used to assess asthma control both in clinical practice and in clinical trials, as it better reflects asthma control in patients with different asthma phenotypes, asthma control levels and on different treatment regimens [26]. Recently, Bateman and colleagues undertook an analysis of five published SMART trials for which sufficient patient diary card data allowed a calculation of GINA guideline control [16, 20, 21, 24, 27, 28]. Only 17.1% of SMART-treated patients achieved acceptable control, with the remainder of patients being either partially controlled (38.7%) or uncontrolled (44.2%). With all levels of control, patients had about 75% chance of remaining similarly controlled in follow-up; as described previously, the best predictor of future control is current control. The low figure of just 17% of patients controlled adequately is in sharp contrast with several population-based surveys of asthma control in Europe and North America, which suggest that current practice results in approximately 40–50% adequate control levels [14, 29–32]. It has been argued that patients were recruited for SMART trials from a background of poor control despite maintenance therapy and may represent a subset of patient with more severe disease. As such, a more appropriate comparator group might be similar to patients as recruited for the GOAL trial, a trial undertaken to determine what proportion of a population of asthma patients can achieve well-controlled status when therapy is adjusted by a specified protocol with the attainment of control in mind [7]. Of 3421 patients

recruited with uncontrolled asthma, 71% of those randomized to titrated ICS/LABA therapy were well-controlled by the end of 1 year, whereas 59% of those randomized to ICS monotherapy were well-controlled. If the comparison is limited to the most severe of the GOAL patients who were poorly controlled at recruitment despite a moderate dose of ICS, the corresponding figures for well-controlled disease were 62% and 47%.

It is well known that many asthma patients may suffer inadequate asthma control, with significant airway inflammation, but be relatively asymptomatic either as a function of their 'non-perceiver status' and/or may simply have adapted to sub-optimal control with frequent symptoms and sub-optimal quality of life. For that reason, acute exacerbation and significant decline in quality of life can occur both in patients with mild and moderate symptom control [26]. Hence, the increased emphasis in international asthma guidelines is not only on current level of asthma control (symptoms, night-time awaking, reliever use, current lung function) but also on estimation of the 'future risk' – that is the potential for experiencing future acute exacerbation, lung function deterioration or medication side effects [26]. In the SMART study meta-analysis for all trial patients, there was a correlation between the level of asthma control and the future exacerbation risk, with the risk doubling for a partially controlled patients vs. a controlled patient, and increasing 6-fold for an uncontrolled patient [27].

The control results from the SMART studies are summarized in Table 1. On average, the patients using the SMART strategy for asthma management used their quick reliever at least once per day, experienced nocturnal symptoms every 7–10 night, were asymptomatic less than 50% of the study time and suffered from severe asthma exacerbation at a rate corresponding to approximately one in five patients per year [10].

Education and self-management plans

National and international guidelines strongly suggest asthma education and provision of written action plans to educate patients about their disease, guide symptom prevention and management of exacerbations [33–37]. All patients with asthma experience episodic, reversible airflow obstruction that can be triggered by a variety of stimuli. In most cases, an exacerbation evolves over a course of days. Prompt recognition and immediate management of impending exacerbation is a key in aborting it and prevents potentially life-threatening asthma attack. However, only minority have or use written action plans that would instruct patients on asthma self-management [14, 36, 37].

Literature supports use of written action plans, based on personal best PEF, symptoms or both, showing lower healthcare utilization [38]. Research shows that not only written asthma plans but also structured asthma education involving educational sessions on strengthening asthma knowledge and self-management skills, familiarization with reliever and maintenance medications, avoidance of exacerbation triggers, education about PEF measurements and interpretation of results and simulation sessions involving discussions of the disease-specific situations and complications with active instructions on the self-management of those situations showed significant benefit in the way of reduction in health care utilization and significant benefit-cost ratio, especially in patients with moderate to severe asthma. When combined with Internet-based education programs, standard patient education programs show even better cost-benefit ratio [39, 40].

Patient education requires teamwork by the physician, registered nurses and trained asthma educators. It appears appropriate that the team-approach to asthma management be initiated by the asthma-treating

Table 1. Asthma control endpoints, baseline and during SMART therapy

Study reference	Rabe et al.	Scicchitano R et al.	O'Byrne PM et al.	Rabe KF et al.	Vogelmeier C et al.	Kuna P et al.	Bousquet et al.
Study duration	6 months	12 months	12 months	12 months	12 months	6 months	6 months
Symptom free days (%)	B: 29.6 T: 55.1	B: 9.8 T: 41.7	B: 23.1 T: 54	B: 9.2* T: 40.3*	N/A	B: 9.3 T: 44.2	B: 10.7 T: 47.2
As-needed reliever use (inhalations/day)	B: 1.64 T: 1.04	B: 1.9 T: 0.90	B: 2.46 T: 1.01	B: 1.8 T: 1.02	B: 2.6 T: 0.59†	B: 2.29 T: 1.02	B: 2.23 T: 0.95
Reliever-free days (%)	B: 24.3 T: 55.3	B: 29.3 T: 59.8	B: 8.2 T: 55	B: N/A T: 52	N/A	B: 8.9 T: 56	B: 10.3 T: 58.2
Nights with awakenings (%)	B: 13.3 T: 6.5	B: 22.6 T: 9.4	B: 21.8 T: 9.0	B: 31.1 T: 14.1	N/A	B: 33.7 T: 14.1	B: 32.1 T: 12.0
Severe Exacerbations (events/patient/year)	0.08	0.23	0.19	0.19	0.24	0.24	0.25

*24 h period.

†For weeks 0–4 (during which morning and evening budesonide/formoterol doses were unchanged at two inhalations of 160/4.5)[10].

B, baseline; T, treatment; NA, not available.

physician, but in reality it appears that many of the asthma-treating physicians are themselves not up to date with the current best practice in asthma education involving strategizing, communication in setting of treatment failure and identifying and addressing the issue of common in chronic diseases management non-compliance. This is reflected in the concerning statistics regarding asthma management strategies gathered from the surveys of the community general practitioners in Canada. It appears that many asthma-treating physicians are not fully aware of the important, guideline-concordant asthma assessment recommendations. Studies show that only 60.5% of children and approximately 45% of adults suffering from asthma reported having ever lung function testing performed by their physicians, even though it is a key component of asthma diagnosis and subsequent disease monitoring and management [29, 31]. Chapman et al. reported that approximately 80% of patients surveyed in their study did not have a written action plan to guide them through handling of their exacerbation and 32% had never demonstrated their inhaler technique to a health practitioner. This may translate into overestimation of asthma control by the physicians and failure to undertake appropriate steps to achieve control, as reflected by one Canadian study where physicians considered only 42% of their patients as uncontrolled, whereas as many as 59% of the study patients suffered from uncontrolled disease as defined by the GINA guidelines [31].

It is suggested by some that an advantage of the SMART strategy is that the medication use is titrated to meet the needs by virtue of the patient's response to symptoms perhaps obviating or minimizing the need for action plans. Thus, the strategy relies strongly on appropriate patient-initiated therapy at first sign of exacerbation. However, the SMART strategy neither specifies the need and pattern of symptom monitoring, nor does it specify an action plan with a stepwise approach at dose titration for the self-treatment strategy. The protocols of SMART studies allowed patients to use up to 8–10 puffs of the reliever medication per day prior to seeking medical help. The level and duration of the high dose of the reliever was also not specified and it remains unclear as to how an action plan would be written for a patient using the SMART treatment strategy.

Asthma control surveys in many developed countries showed that majority of patients have poor disease control [14, 29–31, 41, 42]. Does this mean that our treatment targets are unrealistic? This does not seem to be the explanation as shown by the results of the Gaining Optimal Asthma control (GOAL) study. Investigators in this multi-centre trial recruited poorly controlled asthma patients and treated them for a year using either an ICS or ICS/LABA, titrating treatment doses for symp-

tom prevention. The composite primary end point of asthma control included six parameters including rescue medication use, symptoms, night-time awaking, exacerbations, ER visits and PEF. By the end of the trial, well-controlled disease was seen in the majority of patients, reaching almost 80% in the ICS/LABA treated group [7]. Poor asthma control in clinical studies and in real life may be explained by multiple patient and clinician-related factors, including low patient expectations with respect to achieving symptom control that translates into miscommunication between patients and clinicians which leads in the end to suboptimal asthma control. Also, poor symptom perception and therapy non-adherence can complicate attaining adequate asthma control.

One of the key components of asthma management is a good communication between the treating clinician and the patient. This calls for thorough understanding and communication of the symptoms and asthma control by the patient to the clinician for the clinician to take steps in adjusting therapy to achieve as best a control as possible. However, there appears to be a major discrepancy between patients' perceived control of asthma and reported symptom severity. For example, in the European survey of nearly 3000 asthma patients conducted by Rabe et al., only 5.3% of patients achieved GINA-defined asthma control, but approximately 50% of patients with severe disease perceived their asthma to be well-controlled despite overall poor quality of life and frequent healthcare utilization [29]. It implies that patients often settle for suboptimal symptom control and poor quality of life. Reasons for that remain unclear, but may stem from poor understanding of the illness, a reflection of insufficient education and poor understanding of the severity of illness from both the patient and the physician perspective that translates into insufficient attempts at achieving control. Also, it appears that many asthma-treating physicians are not fully aware of the important, guideline-concordant assessment recommendations. Studies show that only 60.5% of children and approximately 45% of adults reported having ever lung function testing performed by their physicians, even though it is a key component of asthma diagnosis and subsequent disease monitoring and management [39, 40]. Chapman et al. reported that approximately 80% of patients surveyed in their study did not have a written action plan to guide them through handling of their exacerbation, and 32% had never demonstrated their inhaler technique to a health practitioner. This may translate into overestimation of asthma control by the physicians and failure to undertake appropriate steps to achieve control. The SMART therapy, by relying on the presence of breakthrough symptoms to drive a portion of the anti-inflammatory

dosing poses special challenges for educators and physicians who may no longer be pursuing similar pictures of acceptable outcomes. For the physician prescribing the symptom-reactive SMART strategy, frequent use of reliever doses may be considered acceptable, whereas educators following the traditional symptom-preventive strategies may consider the frequent use of reliever doses to be a treatment failure. There may also be confusion about treatment goals and strategies if more than one physician is involved in patient care. A recent review of patient anti-asthma medication in the UK found a small amount of symptom-reactive SMART prescribing with budesonide/formoterol combination inhaler [43]. When examined closely, approximately half of the patients receiving prescriptions for budesonide/formoterol in SMART fashion also had prescriptions for separate short-acting bronchodilator inhalers. It remains unclear from the review whether this confusion arose because more than one physician was involved in patient care or whether the prescribing physician had contaminated the SMART strategy, perhaps failing to understand it fully.

The SMART approach to asthma management strongly relies on patient's accurate perception of worsening asthma as a trigger to supplemental symptom-driven medication dosing. However, several studies have documented a discrepancy between patient symptoms perception and true degree of obstruction. As described by Rubinfeld and Pain, some patients may be 'poor perceivers' with few or no symptoms despite significant airway obstruction [44]. In his study, Rubinfeld tried to induce airway obstruction in 82 patients with either confirmed asthma or occupational asthma. He found that about 15% of patients were asymptomatic even when their FEV₁ had been reduced to less than 50% predicted. Similarly, when Rabe et al. [22] assessed the SMART treatment approach, they found that 86% of the patients failed to take supplemental doses of budesonide/formoterol when PEF fell by 30% or more. Studies have also documented the presence of a different population of patients who may be 'hyper-responsive' and exquisitely sensitive to even minor changes in the airway calibre [45, 46]. Poor correlation between objectively measured airflow and symptoms is a well-documented phenomenon, with only minority of patients using their bronchodilators appropriately and majority of patients either over- or under using it [47]. These findings make appropriate management of the asthma patient even more challenging, calling for a high degree of suspicion and vigilance on part of the physician to avoid missing inadequate control and intervening in time for poorly controlled patients. The importance of the discordant relationship between the asthma symptom perception and true airway obstruction has not been addressed in the symptom-driven

asthma therapy, a key component of the SMART approach. Further studies will be needed to assess its effects.

Some have suggested that symptom-reactive SMART therapy may encourage compliance with controller therapy. Regrettably, electronic monitoring of medication use in the SMART trials has not been used to test this hypothesis. However, previous studies have failed to show that the pharmacologic solution of combining a bronchodilator and an inhaled steroid in a single inhaler encourages compliance by this means. Bosley et al. in the study assessing effect of combining ICS with bronchodilator and using electronic monitoring of dry powder inhalers to assess compliance have shown that treatment was taken on only minority of the study days (30–40%) with only 50–60% of patients taking more than 80% of the prescribed treatment over the whole study period [49]. Compliance was not improved by the administration of the combination formulation.

It appears that treatment compliance is influenced by patient and not medication factors [47, 49]. Poor day-to-day control of asthma symptoms reported in the SMART-treated patients could therefore reflect both. The subset of asthma patients enrolled in the SMART studies (poorly controlled asthmatics) who remain poorly compliant with their day-to-day asthma therapy as reflected in overall poor daily symptom control, may resort to urgent self-treatment of exacerbations by supplemental doses of ICS/KLABA, with a reduction in protocol defined 'exacerbations' against a background of frequent and disabling day-to-day symptoms.

Long-term outcomes

Recently, investigators have found higher sputum and bronchial biopsy eosinophil counts after 1 year in patients using budesonide/formoterol in the symptom-reactive SMART fashion (two puffs twice daily plus as needed) when compared with traditional symptom-preventive, constant dose budesonide/formoterol (with budesonide dose of 1600 mcg per day) [50]. No difference was observed the fraction of exhaled nitric oxide, total number of inflammatory cells, activated CD4+ (TH cells) and thickness of basement membrane (a marker of remodelling). Effects of SMART therapy on remodelling remain unknown at present, and long-term studies will be needed to assess its efficacy in overall asthma control.

In summary

Clinical studies show that low-dose budesonide/formoterol combination used in the SMART fashion with symptom-reactive supplemental dosing can reduce

asthma exacerbations when compared with the use of budesonide alone or to low doses of budesonide/formoterol without supplemental dosing. Patients treated with this strategy appear to be under-treated in that the majority fail to achieve guideline-defined control standards. The SMART strategy has not been tested against equivalent or higher doses of budesonide/formoterol given in symptom-prevention fashion. Existing educational strategies that focus on recognition of poor disease control may not be applicable with SMART

therapy, and the use of action plans has not been clarified with this symptom-reactive strategy. There is some evidence from pharmacy database review that the current use of SMART therapy may fail to mirror clinical trial design with the frequent contamination of the strategy with short-acting bronchodilators. There is no information on long-term outcomes with a symptom-reactive ICS/LABA strategy, but one report shows that after a year of SMART therapy, sputum and airway biopsy eosinophil counts rose.

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