Title: "As-needed" inhaled corticosteroids for patients with asthma

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Asthma pharmacotherapy, as-needed, reliever, rescue, intermittent, asthma management, asthma exacerbations, asthma control, SMART, PARTICS, AIR

Abbreviations:

ACQ: asthma control questionnaire
ACT: asthma control test
AIR: anti-inflammatory reliever
BDP: beclometasone dipropionate
CI: confidence interval
DPI: dry-powder inhaler
EIB: exercise-induced bronchoconstriction
FDA: US Food and Drug Administration
FeNO: fractional exhaled nitric oxide
FEV1: forced expiratory volume in the first second
GINA: Global Initiative for Asthma
HR: hazard ratio
ICS: inhaled corticosteroids
LABA: long-acting beta2 adrenergic agonist
LAMA: long-acting muscarinic antagonist
LTRA: leukotriene receptor antagonist
MART: Maintenance And Reliever Therapy (with ICS-formoterol)
NAEPP: National Asthma Education and Prevention Program
OCS: oral corticosteroids
PARTICS: Patient **A**ctivated **R**eliever **T**riggered **I**nhaled **C**ortico**S**teroids
PEF: peak expiratory flow
pMDI: pressurized metered dose inhaler
SABA: short-acting beta2 adrenergic agonist
SAMA: short-acting muscarinic antagonist
SMART: Single Maintenance And Reliever Therapy

Abstract:

Prevention of severe asthma exacerbations is a primary management goal for asthma across the severity spectrum. Inhaled corticosteroids (ICS) decrease the risk of asthma exacerbations, but patient adherence to ICS-containing medications as a daily maintenance therapy is poor, and many patients overuse short-acting beta2-agonist relievers; both are associated with increased risk of severe exacerbations and death. Airway inflammation also varies over time, influenced by exposures such as viral infections and allergen. As-needed ICS strategies, in which patients receive ICS (or additional ICS, if already taking controller therapy) whenever they take their reliever inhaler, empower patients to adjust their ICS intake in response to symptom fluctuation. These strategies can improve asthma morbidity outcomes, particularly by reducing severe exacerbations and reducing the risk of adverse effects of oral corticosteroids. In this review, the evidence for combination ICS-formoterol in a single inhaler, ICS and short-acting beta2-agonists in separate inhalers, and combination ICS-albuterol in a single inhaler is presented, along with practical considerations, evidence gaps, and implications for clinical practice for each strategy, presented by level of asthma severity and age group. Improving access to such strategies on a global scale is imperative in order to improve asthma outcomes and achieve equity across populations.

INTRODUCTION:

Prevention of asthma exacerbations is an increasing focus of attention, not only because of their burden on patients and the health system[1], but also because of the need to minimize exposure to the adverse effects of oral corticosteroids (OCS)[2], and the risks of regular use[3] and over-use of short-acting beta2-agonist (SABA) relievers[4]. These risks are seen across the asthma severity spectrum; patients with mild asthma can still have severe or even fatal exacerbations[5]. Airway inflammation is present across all asthma severity levels, and viral infections, allergen exposure, and pollution can increase or modify this inflammation[6]. Inhaled corticosteroids (ICS) are highly effective in reducing the risk of exacerbations[7], but patients are often poorly adherent with maintenance treatment[8], relying on SABA for symptom relief and only starting or increasing their controller medication or presenting for medical care when an exacerbation is already well-established[9]. This reinforces the need for flexible treatment regimens that allow day-to-day adjustment of the anti-inflammatory treatment dosage, rather than relying only on occasional clinic visits for optimizing each patient's medication regimen.

In the early 2000s, multiple studies challenged the long-standing conventional approach of prescribing regular maintenance ICS-containing treatment plus SABA for symptom relief.[10-13] Since then, substantial evidence has accumulated in both mild and moderate/severe asthma about 'anti-inflammatory reliever' (AIR) regimens, in which patients receive ICS (or additional ICS, if already taking controller therapy) whenever they take their reliever inhaler.

This review considers three such as-needed regimens: ICS-formoterol in a single inhaler, ICS and SABA in separate inhalers, and ICS-albuterol in a single inhaler. These approaches must be distinguished from episodic use of regular high-dose ICS after asthma has worsened. What is the evidence for as-needed combination ICS-formoterol and as-needed combination ICS-albuterol in patients with mild or moderate/severe asthma? If these

combinations are not available or if patients regularly use reliever nebulization, what evidence is available about an AIR approach using separate ICS and SABA inhalers? This article presents the evidence about these three treatment regimens, and discusses their strengths and limitations, including practical issues, summarized in **Table 1**.

1. COMBINATION ICS-FORMOTEROL IN A SINGLE INHALER

(a) Mild asthma

SOMA[14] was a double-blind, 6-month study in 92 patients with 'intermittent' asthma and elevated fraction of exhaled nitric oxide (FeNO, ≥20 ppb). Patients were randomized to as-needed budesonide-formoterol (160/4.5mcg) or as-needed formoterol 4.5mcg, for symptom relief and pre-exercise. ***Outcomes***: FeNO reduction (primary outcome) was significantly greater with as-needed budesonide-formoterol than as-needed formoterol, 18.3ppb vs 2.8ppb respectively ($p<0.001$). Change in lung function was significantly greater.

Lazarinis et al[15] investigated as-needed ICS-formoterol for symptom relief and pre-exercise use in a double-blind study of 66 patients ≥12 years with mild asthma and exercise-induced bronchoconstriction (EIB). ***Outcomes***: At 6 weeks, as-needed low-dose budesonide-formoterol was superior to as-needed SABA and non-inferior to daily ICS for reducing EIB.

SYGMA 1[16] was a double-blind, placebo-controlled, 12-month study in 3,849 patients aged ≥12 years with asthma that was uncontrolled on SABA alone or controlled on low-dose ICS or LTRA. Patients were randomized to as-needed budesonide-formoterol 160/4.5mcg, as-needed terbutaline, or twice-daily budesonide 160mcg plus as-needed terbutaline. ***Outcomes***: As-needed budesonide-formoterol was superior to SABA but inferior to budesonide for well-controlled asthma weeks (primary outcome). However, it reduced the risk of severe exacerbations by 64% vs. SABA alone, and similar to maintenance ICS despite 83% lower ICS dose. There were small differences in ACQ-5 and FEV1 vs. maintenance ICS.

SYGMA 2[17] was a double-blind, placebo-controlled, 12-month study in 4,215 patients meeting the same eligibility criteria as SYGMA 1. This study was more pragmatic, without electronic diaries or reminders. Patients were randomized to as-needed budesonide-formoterol or twice-daily ICS plus as-needed SABA. ***Outcomes***: As-needed budesonide-formoterol was non-inferior to maintenance ICS for severe exacerbation rate (primary outcome), with 75% lower median daily ICS dose. Small differences were seen in ACQ-5 and FEV1.

Novel START[18] was an open-label, more pragmatic study in 675 adults taking SABA alone, with similar randomization groups as SYGMA 1. ***Outcomes***: As-needed budesonide-formoterol showed a similarly large (60%) reduction in risk of severe exacerbations compared with SABA alone; severe exacerbations were also significantly lower than with regular ICS. Differences in symptom control, FEV1 and FeNO were clinically unimportant.

PRACTICAL[19] was an open-label study in 890 patients taking SABA alone or low/medium dose ICS. Patients were randomized to as-needed budesonide-formoterol or twice-daily ICS plus as-needed SABA. ***Outcomes***: As-needed budesonide-formoterol showed a significant reduction (31%) in severe exacerbations compared with maintenance ICS (primary outcome), with lower average ICS dose.

A Cochrane meta-analysis[20] of the previous four studies in mild asthma (n~10,000) found a 65% reduction in ED visits/hospitalizations compared with as-needed SABA, and 37% reduction compared with regular ICS plus as-needed SABA.

Based on this evidence, as-needed low-dose ICS-formoterol has been recommended by GINA for treatment of mild asthma since 2019,[21,22] and has been approved by regulators in >35 countries, although not by the US Food and Drug Administration (FDA). Studies of as-needed ICS-formoterol were not evaluated for the 2020 US asthma guideline focused update[23].

In subgroup analyses of Novel START[18] and PRACTICAL[19], no significant predictors of better response to regular ICS than as-needed ICS-formoterol, including FeNO and blood eosinophils, were identified. However, in the SYGMA studies, patients previously taking SABA alone experienced greater reductions in severe exacerbations with as-needed ICS-formoterol than with regular ICS[18,24]. Pooled data for 889 adolescents in SYGMA 1 and 2[25]showed a 77% reduction in severe exacerbations vs as-needed SABA, and similar reduction to daily ICS. In younger adolescents, there was a significantly greater increase in height with as-needed ICS-formoterol than with daily low-dose ICS[25].

Qualitative research embedded in Novel START and PRACTICAL[26-28] found that most patients (but not all) preferred as-needed combination ICS-formoterol over maintenance ICS plus as-needed SABA.

(b) Moderate-severe asthma

Use of combination ICS-formoterol as both Maintenance And Reliever Therapy is called MART or SMART. This regimen has been established worldwide for treatment of moderate/severe asthma for >15 years, approved with budesonide-formoterol by regulators in >120 countries (AstraZeneca, personal communication), and with beclometasone-formoterol in >70 countries (Chiesi, personal communication), although not in the US. In 2020 SMART was recommended by the NAEPP guidelines as the preferred treatment for Steps 3-4 for adults, adolescents and children ≥4 years.[23] Authors from the NAEPP Expert Panel and GINA recently published a practical guide to SMART.[29]

The evidence base for the safety and efficacy/effectiveness of SMART compared with same or higher dose ICS or ICS-LABA plus as-needed SABA is too extensive to itemize here, comprising 10 double-blind clinical trials (n=18,367), >16 open-label studies (n=23,361), and several meta-analyses.[30-32] In patients with a history of 1+ severe exacerbations in the previous year (therefore at higher risk of future exacerbations) SMART reduced the risk of severe

exacerbations by 32% (risk ratio [RR] 0.68 (95%CI 0.58--0.80) compared with same dose ICS-LABA plus as-needed SABA, and by 23% (RR 0.77 (95%CI 0.60—0.98) compared with higher dose ICS-LABA, with similar or better asthma symptom control.[30] Exacerbation reduction in adolescents was even greater.[33] In open-label studies in patients *not* selected for poor symptom control or history of exacerbations, SMART reduced severe exacerbations by 17% (odds ratio [OR] 0.83 [95%CI 0.70—0.98]) compared with conventional best practice.[32] In a study with electronic inhaler monitoring, there was less reliever over-use with SMART vs. SABA reliever.[34]

Children: STAY

The double-blind STAY study included 341 children aged 4-11 years, randomized to budesonide-formoterol 80/4.5mcg once-daily and as-needed, or once-daily budesonide-formoterol plus as-needed SABA, or high dose budesonide (320mcg) plus as-needed SABA.[35] SMART reduced the risk of severe exacerbations by 70 and 79% with SMART versus high-dose budesonide and low-dose budesonide-formoterol respectively, both $p<0.001$. Symptoms were significantly less with SMART, and growth was 1.0 cm greater vs. high-dose budesonide.

There have been limited subgroup analyses of SMART studies. In one analysis, patients with high baseline SABA use were at particularly high risk of severe exacerbations with conventional treatment.[36] In one study in patients poorly adherent to maintenance controllers, SMART increased their average ICS dose compared with conventional therapy..[37] In another study, SMART with BDP-formoterol was more effective for severe exacerbations than conventional therapy across blood eosinophil levels, but with greater benefit with higher eosinophils.[38]

2. ICS + ALBUTEROL IN SEPARATE INHALERS

(a) Mild asthma

Adults:

BASALT[39] was a placebo-controlled, 9-month clinical trial in 342 adults with mild-to-moderate asthma well-controlled on low-dose ICS, randomized to 6-weekly physician-based or 6-weekly FeNO-based ICS adjustment, or symptom-based adjustment (taking 2 puffs of beclometasone 40mcg for every 2 puffs of albuterol). To achieve blinding, patients used 4 inhalers throughout the study. ***Outcomes***: Time to treatment failure (primary outcome) was not significantly different between groups, but failure rates were lowest in the as-needed ICS+SABA group (15%) and highest with physician-based adjustment (22%), despite having half the mean monthly ICS dose.

Children:

TREXA[40] was a double-blind, placebo-controlled, 10-month trial in 288 children/adolescents aged 5-18 years with mild persistent asthma well-controlled on low-dose ICS; the as-needed SABA and ICS/placebo inhalers were taped together. Participants were randomized to (a) regular beclometasone plus as-needed ICS+SABA, (b) regular beclometasone plus as-needed SABA, (c) as-needed ICS+SABA, and (d) as-needed SABA (placebo group). ***Outcomes***: Time to first severe exacerbation (primary outcome) was significantly lower compared with placebo for both maintenance ICS groups, but not significantly lower with as-needed ICS+SABA. However, treatment failures were significantly lower with as-needed ICS+SABA without the lower growth rate (1.1 cm) seen with daily ICS.

ASIST[41] was a pragmatic, open-label, 12-month, primary care study in 206 African American children aged 6-17 years with well-controlled asthma stabilized on low-dose ICS. They were randomized to physician-based ICS adjustment or symptom-based adjustment (taking ICS whenever SABA was taken). ***Outcomes***: Change in Asthma Control Test (ACT) or Childhood ACT (primary outcome) was not significantly different between groups, nor were exacerbations or lung function, despite much lower ICS dose.

(b) Moderate-severe asthma

Adults:

PREPARE[42] was a single-blind, randomized, 15-month, pragmatic trial in 1,201 Black or Latinx patients with uncontrolled asthma (mean ACT ~15) or a history of asthma exacerbations, despite ICS±LABA or additional controllers. At enrollment, self-reported adherence was good; lung function was not measured. Patients were randomized to continue their usual controllers and relievers (SABA and/or short-acting muscarinic antagonist (SAMA)) or to use 80mcg beclometasone, 1 puff for each reliever puff, or 5 puffs per nebulization while continuing their usual controllers and relievers; the regimen was called PARTICS (Patient Activated Reliever-Triggered Inhaled CorticoSteroids). Many patients had very poorly controlled asthma, and many were regularly using nebulized SABA. ***Outcomes****:* Compared with usual care alone, intervention group participants had a 15.4% reduction in risk of severe asthma exacerbations (hazard ratio (HR), 0.846; 95%CI, 0.72–0.999; p=0.048), greater improvement in symptom control (mean ACT score increases of 3.4 vs. 2.5 points, respectively; minimal clinically important difference = 3), and 20% fewer days lost from school, work, or usual activities. Their modestly higher average ICS dispensing (1.1 inhalers/year) reflected receipt of 3.5 study ICS inhalers but lower self-reported dispensing of usual controllers (5.4 vs 7.8 inhalers/year).

It remains to be seen whether this strategy is similarly effective in men, since 85% of PREPARE participants were women.

There have been no studies using separate as-needed ICS and bronchodilator inhalers in children with moderate-severe asthma.

3. COMBINATION ICS + ALBUTEROL IN A SINGLE INHALER

(a) Mild asthma

Adults:

BEST[13] was a 6-month, double-blind, placebo-controlled, trial in 455 patients aged 18-65 years whose asthma was controlled after 4-weeks on low-dose ICS. They were randomized to as-needed combination beclometasone(250µg)-albuterol(100µg); as-needed albuterol; twice-daily beclometasone plus as-needed albuterol; and twice-daily combination beclometasone-albuterol plus as-needed albuterol. The primary outcome was average morning peak expiratory flow (PEF) over weeks 23-24. ***Outcomes***: End-study morning PEF was higher by 8 L/min (P=0.04) and the exacerbation rate was lower (0.74 vs 1.63/year, P<0.001) with as-needed combination ICS-SABA than with as-needed SABA, with a lower cumulative ICS dose. Outcomes with as-needed combination ICS-SABA were not significantly different from regular ICS plus as-needed SABA or regular combination ICS-SABA plus as-needed SABA, except that the exacerbation rate was higher with regular combination ICS-SABA (1.76/year) than with regular ICS (0.71/year) or as-needed combination ICS-SABA (0.74/year).

There are no studies with as-needed combination ICS-SABA single-inhaler in children with mild asthma.

(b) Moderate-severe asthma

Adults and children:

MANDALA[43] was a double-blind, randomized, event-driven study, in 3,132 patients ≥4 years old with uncontrolled (ACQ-5 ≥1.5) moderate/severe asthma and ≥1 severe exacerbation in the previous year, despite medium/high-dose ICS or low/high dose-ICS-LABA. Patients were randomized to take as-needed albuterol-budesonide 180/160µg (only adults/adolescents), 180/80µg albuterol-budesonide, or albuterol 180µg via pMDI, in addition to their regular maintenance treatment. The trial continued until ≥570 severe exacerbations were reported, with minimum duration 24-weeks. The primary outcome was time to first severe exacerbation for both doses of albuterol-budesonide vs albuterol. ***Outcomes***: Compared with as-needed albuterol plus usual maintenance therapy, the severe exacerbation risk was reduced by 27%

(HR 0.74 [95%CI 0.62—0.89], p=0.001) with as-needed albuterol-budesonide 180/160µg, and by 17% (HR 0.84 [95%CI 0.71—1.00], p=0.052) with as-needed albuterol-budesonide 180/80µg. Compared with as-needed albuterol, the annualized total OCS exposure was reduced by 33% and 25%, respectively. At week 24, an ACQ-5 decrease of 0.5 was seen in 66.8% and 64.7% patients with higher and lower dose SABA-ICS respectively, compared with 62.1% and 61.6% respectively with as-needed SABA. These differences were statistically significant only for the higher dose SABA-ICS (OR 1.22 [95%CI 1.02—1.47] but not the lower dose SABA-ICS (OR 1.13 [95%CI 0.95—1.35]). Mean self-reported adherence with maintenance therapy was 75% in all three groups. Adverse events were similar between treatment groups. Only 83 children 4-<12 years and 100 children 12-<18 years were randomized, with no significant differences in severe exacerbation risk between as-needed combination ICS-SABA and as-needed SABA alone in these age groups.

DISCUSSION:

There are now three as-needed ICS strategies available, with varying levels of evidence for their efficacy, effectiveness, and safety, that can improve asthma outcomes while reducing exposure to and adverse effects from OCS and SABA reliever overuse. Practical considerations, evidence gaps, and implications for clinical practice are discussed below, and summarized in Table 1.

<u>Combined ICS-formoterol in a single inhaler</u>

The substantial reductions in severe asthma exacerbations demonstrated for as-needed ICS-formoterol alone in mild asthma and as SMART in moderate-severe asthma, as well as its proven safety record, translate to large reductions in healthcare utilization at a population level

with lower or slightly increased ICS dose. Use of ICS-formoterol for both maintenance and relief allows seamless step-up and step-down between treatment steps according to clinical need, without changing the patient's inhaler.

With regard to choice between treatment regimens in mild asthma, the lack of significant baseline predictors of better response to regular ICS than as-needed ICS-formoterol indicates that phenotyping is not needed when initiating as-needed ICS-formoterol in mild asthma. However, patients with mild asthma previously taking SABA alone are likely to do better with as-needed ICS-formoterol than with regular ICS[24], perhaps due to lack of established adherence behavior. This may be particularly important in adolescents, given their known poor adherence to maintenance controller therapy, and the lack of effect of as-needed ICS-formoterol on height in this age group compared with daily low-dose ICS would remove a potential concern for parents and patients[25]. In moderate-severe asthma, no sub-populations have been identified that do better with conventional maintenance therapy plus as-needed SABA than with SMART. However, qualitative research indicates that shared decision-making is important for any treatment choice.

Although some clinicians are concerned about the potential risk of desensitization with over-use of formoterol compared with albuterol[44 45] this has not been demonstrated on human airway smooth muscle cells,[46,47] and is not supported by the strong demonstrated safety record for as-needed ICS-formoterol in both mild and moderate-severe asthma,[48] and contrasts with the strong evidence for risks of hospitalization and death with even modest overuse of SABA.

Multiple ICS-formoterol combinations are available internationally, but in the US, ICS-formoterol combinations are available only with budesonide or mometasone. Mometasone-formoterol has not been tested as SMART in clinical trials. Neither formulation is FDA-approved for acute asthma symptom relief, which currently imposes barriers to access from some insurance companies, pharmacies, and may represent a legal liability,[49] although there are also

potential liabilities with prescribing against NAEPP guideline recommendations. Despite the strong evidence for SMART, its implementation has been incomplete, reflecting the primacy of SABA as reliever in many health systems.

Cost-effectiveness analyses identify cost savings relative to alternative therapies with the use of SMART in moderate/severe asthma and of as-needed ICS-formoterol in mild asthma due to its reduction in asthma exacerbations[50]. No evidence about cost-effectiveness is yet available for the other as-needed ICS strategies considered in this review.

We consider that SMART as an as-needed ICS strategy should be employed whenever possible to reduce asthma therapy regimen complexity, improve adherence and reduce severe exacerbations. Many reasons, seemingly unique to the US healthcare and regulatory system, underlie the deficient implementation and dissemination of SMART despite ample evidence of its efficacy in improving asthma outcomes. First, the FDA has rejected data from Turbuhalers, with which all but two of the SMART studies were performed. Consequently, the FDA-approved Product Information states to this day that budesonide/formoterol cannot be used to relieve bronchoconstriction. Presumably, pharmaceutical companies have not been financially incentivized to conduct the additional studies that would grant a reliever indication to ICS/formoterol with FDA-approved devices. Second, the 13-year delay between EPR3 (at which time only 1 SMART study had been published) and the 2020 focused update prevented the timely update of American asthma guidelines with SMART efficacy and effectiveness data. Finally, some clinicians were concerned with LABA safety due to excess asthma-related morbidity and mortality from the use of LABA monotherapy without ICS, and extrapolated this to SMART. Even after expensive, FDA-mandated large clinical trials demonstrated the safety of ICS-LABA controller therapies and removed the black box warning for ICS/LABA formulations, and despite the extensive safety record demonstrated in SMART trials, some of this concern apparently persists.

ICS and SABA in separate inhalers

In mild asthma, taking ICS whenever SABA is taken might provide similar protection from asthma exacerbations and similar symptom control compared with daily ICS use with as-needed SABA, with much lower average ICS doses and in children, potentially greater growth over 12 months. However, the four studies supporting this strategy in mild asthma were small, and all were 'step-down' studies, i.e., in patients with well-controlled asthma on low-dose ICS or similar treatment. Current NAEPP guidelines[23] recommend as-needed concomitant ICS and SABA for adults with mild persistent asthma (step 2), but not children. Practical issues include the difficulty of carrying multiple inhalers and potential selective non-adherence with the ICS inhaler. However, qualitative research in ASIST indicated that parents felt more in control of their child's asthma with symptom-based ICS adjustment, compared with physician-based adjustment.

Providing add-on ICS for use whenever SABA±SAMA was taken also reduced asthma exacerbations in Black and Latinx adults with moderate-severe asthma[42]—populations that experience >2-fold greater rates of asthma-related ER visits and mortality[51,52]. This regimen can be adjusted for use with nebulized SABA±SAMA, although it would be desirable to improve asthma management in such patients, given the increased risk of serious exacerbations and asthma death with nebulized SABA.[53,54]

This regimen has the disadvantage of requiring separate as-needed inhalers which adds to regimen complexity, which is a risk factor for poor inhaler technique and non-adherence[55]. However, this strategy is not restricted to any specific controller therapy regimen, which may facilitate its relevance and uptake for patients whose health insurance plan (or lack of one) may dictate specific controller therapy regimens, including those who do not have access to combination ICS-SABA or ICS-formoterol.

Dissemination, implementation, and adoption of this regimen in large healthcare systems and broader populations needs to be investigated.

The costs to the healthcare system of administering an average 1.1 ICS inhalers per patient per year would be relatively small.

Combined ICS-albuterol in a single inhaler

As-needed combination ICS-SABA can be used as reliever in addition to any ICS-containing maintenance treatment in patients with moderate-severe asthma. If approved in the US, this therapy would overcome the currently limited insurance coverage of as-needed ICS-formoterol, broaden AIR options and reduce exacerbation risks, and would avoid the complexity of ICS and SABA in separate inhalers. Albuterol is the most commonly used reliever medication worldwide, most commonly as a pMDI, and providing as-needed combination ICS-SABA pMDI to patients with moderate-severe asthma would avoid the need for changing their as-needed inhaler device, but still requires patients to have separate maintenance and reliever inhalers.

This strategy has the potential to shift current asthma treatment paradigms by avoiding risks associated with use of SABA alone and SABA overuse, although the risks of high use of ICS-SABA still need to be examined. Further evidence is needed about efficacy and safety of this regimen in children. There is also a paucity of data for safety and efficacy of ICS-SABA in mild asthma, which is particularly noteworthy in the US where NAEPP guidelines recommend SABA-only treatment for mild asthma. Additional evidence is also needed to guide recommendations about safe maximum daily doses of ICS-SABA, given the increasing evidence about hazards of even modest levels of SABA over-use across asthma severity.[56,57]

An obvious critical practical issue is that combination ICS-albuterol is not currently available in the US; older formulations are available in a few countries but approved for as-needed use in mild asthma in only a few. The new formulation of budesonide-albuterol used in

MANDALA was administered through pMDI inhalers, which will be phased out in many countries according to the European Commission's protocol due to their fluorinated greenhouse gas content[58].

All as-needed ICS strategies

The mechanism by which as-needed ICS strategies improve asthma morbidity outcomes is unclear, but likely relates to early increases in ICS administration at asthma exacerbation onset, as was long ago speculated for SMART[12,] and is supported by the reduced risk of severe exacerbations after even 1-2 days of as-needed doses of ICS-formoterol[59-61], although additional mechanisms likely distinguish each strategy.

Post hoc analyses thus far suggest that SMART is more effective than conventional therapy with as-needed SABA even in patients with low baseline FeNO and blood eosinophil levels, although it may possibly work even better among patients with higher blood eosinophil levels[38,62], who are at greater risk of asthma exacerbations; patients with lower eosinophil levels may not respond well to fixed dose ICS and SABA[18]. We speculate that these data would apply similarly to the other 2 strategies considering their similar mechanism of action.

As-needed ICS strategies have not been adequately compared to biomarker-directed maintenance strategies, but in the single such study (BASALT), taking ICS whenever SABA was taken performed as well as or better than treatment guided by frequent (6-weekly) FeNO measurement; the latter would have significantly greater healthcare costs.

Not all patients like SMART therapy, and there are potential risks to switching patients to SMART from other controller therapy regimens. The advantage of ICS/albuterol combined in a single inhaler and ICS and SABA in separate inhalers is that patients continue using the same "blue" reliever inhaler they were used to, but now supplemented with ICS.

Although use of as-needed ICS-formoterol, either alone or as SMART, has led to numerically greater reductions in severe exacerbations relative to as-needed albuterol compared with the other two strategies, direct comparisons are not possible because of differences in populations and study designs across trials. No head-to-head trials have compared the efficacy or effectiveness of these three strategies, but such studies would be of global importance. There is also a dearth of data about which as-needed ICS strategy would be appropriate for patients with severe asthma receiving combination ICS/LABA/LAMA inhalers or biologic therapy. Pragmatic trial designs that apply real-world conditions may reveal important differences between each strategy in drug availability, healthcare insurance coverage, participant adherence and understanding of the strategy, etc., that may impact effectiveness. The populations and contexts in which each of these as-needed ICS-bronchodilator strategies are most effective and practical remain to be determined.

CONCLUSION:

As-needed strategies that provide ICS whenever the patient receives reliever medication decrease severe asthma exacerbations compared with using a SABA reliever. These strategies empower patients with the management of asthma symptom fluctuations and, based on the evidence presented in this review, are likely to reduce healthcare utilization and risks of exposure to the cumulative adverse effects of OCS at a population level. Additional evidence is needed about optimal treatment responder characteristics for each of these regimens, to facilitate treatment choice, but shared decision-making remains essential. The adoption of such regimens may be most easily ensured in health systems that have budgetary power over both medications and ED/hospitalizations. However, advocacy to achieve equitable access to effective asthma medications globally, including in the US, is paramount.[63]

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MILD ASTHMA (as-needed medication alone, without maintenance controller)					
As-needed combination ICS-formoterol		**As-needed combination ICS-albuterol**		**As-needed ICS+SABA (separate inhalers)**	
Strengths[1]	***Limitations***	***Strengths[2]***	***Limitations***	***Strengths[3]***	***Limitations***
• Large reduction in severe exacerbations vs SABA alone • Reduction in ED visits/ hospitalization vs daily ICS, with lower ICS dose • In young adolescents, greater growth vs daily ICS[4] • Extensive efficacy and safety data (n~10,000)	• All studies used dry powder inhalers • No data in children <12 years	• Reduction in severe exacerbations vs SABA alone (but not vs daily ICS)	• Very limited data for safety and efficacy • No data in children or adolescents <18 yrs • No studies with dry powder inhalers	• Adults: reduction in severe exacerbations vs daily ICS (not studied vs SABA alone) • Children/adolescents: no significant reduction in severe exacerbations vs SABA alone; similar severe exacerbations as with daily ICS, with lower ICS dose and greater growth	• Very limited data for safety and efficacy • No studies with dry powder inhalers
Practical issues • Easy for patients to use • Simple transition to SMART if daily controller needed • Approved in 35 countries; not by FDA		***Practical issues*** • Easy for patients to use • Available in a small number of countries; approved for as-needed use in mild asthma in some of these		***Practical issues*** • Difficulty for patients of carrying and using two inhalers • Potential non-adherence with the ICS inhaler • ICS not approved for as-needed use	
MODERATE-SEVERE ASTHMA (as-needed medication added to patient's controller therapy)					
As-needed combination ICS-formoterol		**As-needed combination ICS-albuterol**		**As-needed ICS+SABA (separate inhalers)**	
Strengths[5]	***Limitations***	***Strengths[6]***	***Limitations***	***Strengths[7]***	**Limitations**
• Reduction in severe exacerbations with ICS-formoterol SMART, vs same or higher dose of ICS or ICS-LABA plus as-needed SABA, with same or lower total dose ICS • In children, greater growth vs daily ICS plus as-needed SABA[8] • -Extensive data on efficacy and safety (~30,000 patients in RCTs)	• Most studies used dry powder inhaler • No evidence about safety or efficacy of using as-needed ICS-formoterol with non-formoterol ICS-LABA	• Reduction in severe exacerbations vs usual controller plus as-needed SABA	• Studied only in patients with poorly-controlled asthma • No studies with dry powder inhalers	• Reduction in severe exacerbations vs controller plus as-needed SABA or SAMA	• Limited safety data; no spirometric data • Studied only in adult Black and Latinx populations in the US, with poorly controlled asthma • Patients took less of their prescribed controller
Practical issues • Easy for patients to use • Single inhaler • For patients already on daily controller plus as-needed SABA, requires switching from previous inhaler(s) • Not studied with nebulizer • Combination ICS-formoterol available in most countries • SMART is approved in 120 countries, not by FDA		***Practical issues*** • Easy for patients to use • Patients required to have two inhalers • Potential errors in inhaler technique if controller and reliever are in different inhaler devices • Not studied with nebulizer • Combination ICS-SABA approved for as-needed use in a small number of countries, not by FDA		***Practical issues*** • Patients are required to have three inhalers • Difficulty of carrying two inhalers for use outside the home • Potential errors in inhaler technique if SABA, ICS and/or controller are in different inhaler devices • Can be used by patients who frequently use SABA or SAMA nebulizers • ICS not approved for as-needed use	

ED: emergency department; FDA: Food and Drug Administration; ICS: inhaled corticosteroid; RCTs: randomized controlled trials; SABA: short-acting beta2-agonist; SABA: short-acting muscarinic antagonist; SMART: Single inhaler Maintenance And Reliever Therapy with ICS-formoterol

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