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Title: As-needed anti-inflammatory reliever therapy for asthma management: evidence and practical considerations

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ABSTRACT

Asthma is a chronic respiratory disease in which airway inflammation is a key feature, even in the milder expressions of the disease. The conventional pharmacological approach to mild asthma has long relied on reliever therapy with as-needed short-acting beta-agonists (SABA), while anti-inflammatory maintenance with inhaled corticosteroids (ICS) has been reserved for patients with more persistent asthma. Poor adherence to maintenance treatment is an important issue in asthma management, and can partly explain suboptimal symptom control. Over-reliance on SABA bronchodilators for rapid symptom relief is common in real life and potentially leads to an increased risk of asthma morbidity and mortality. Combined anti-inflammatory and reliever medications in a single inhaler have the potential to overcome these limitations. Recent studies in patients with mild asthma have shown that anti-inflammatory reliever therapy with budesonide-formoterol, given on an as-needed basis, is superior to SABA in ensuring asthma control, and non-inferior to budesonide maintenance therapy in preventing exacerbations. To address the implications of these important findings for the management of patients with asthma, Italian specialists convened at a series of meetings held during the second half of 2018 across Italy. This article presents their position on these topics, and includes a review of the evidence supporting the use of anti-inflammatory reliever therapy in mild asthma and the implementation of this novel approach in clinical practice.

Keywords:

Pharmacology and pharmacogenomics, Pneumology, Asthma

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1. INTRODUCTION

Asthma is the most prevalent chronic respiratory disease worldwide.[1] A major cause of absenteeism from school and work, asthma is associated with very high health care expenditure.[2] Key features of asthma include chronic airway inflammation and airway hyper-responsiveness.[3-5] Chronic airway inflammation is present in newly diagnosed disease and in those with mild asthma who have infrequent symptoms.[6-8]

The main goals of asthma treatment are the achievement of good symptom control, the maintenance of normal activity levels, and the minimization of the risk of exacerbations and the development of fixed airflow limitation.[9] Pharmacological therapies generally involve controller medication – mostly inhaled corticosteroids (ICS) for the treatment of the underlying inflammation – and reliever medication – i.e. rapid acting bronchodilators for quick symptom relief, or rescue therapy.[9]

The Global Initiative for Asthma (GINA) document recommends a 5-step approach in which treatment is stepped up or down based on the level of symptom control, so that patients receive the minimum effective treatment.[9] Short-acting beta-agonists (SABA) have traditionally been proposed as rescue medication (i.e., for as-needed use) for all patients with asthma. Conventional regimens for persistent asthma involve daily maintenance therapy with ICS, with or without a long-acting beta-agonist (LABA), and as-needed rescue therapy with a SABA. As-needed SABA alone has been recommended for patients with mild “intermittent” asthma (GINA step 1). Of note, the major revision of the GINA guidelines in 2014 introduced the recommendation to start regular daily controller treatment in patients with infrequent symptoms (i.e. more than twice/month) and proposed regular low-dose ICS as an alternative to SABA in step 1.[2]

Evidence from surveys has shown that asthma often remains poorly controlled despite the availability of effective medications.[10-13] An important issue in the management of asthma, which may partly explain suboptimal control, is the generally poor adherence to maintenance pharmacotherapy with controller therapy.[12,14] Furthermore, a series of paradoxes in conventional asthma treatment have been highlighted in recent publications, questioning the use of SABA alone in step 1 and some potentially misleading messages concerning the safety of SABAs and LABAs.[15]

Over the past two decades, considerable effort has been devoted to the development of alternative treatment strategies to address these unresolved issues and paradoxes in

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conventional asthma treatment.[15-18] An important improvement has been the development of approaches that combine controller (anti-inflammatory) and reliever (rapid-onset bronchodilator) medications in a single inhaler used on top of the maintenance dose of the same ICS-LABA combination used regularly as controller (e.g., budesonide in combination with formoterol, an LABA with an onset of action as rapid as that of the SABA, salbutamol): this is the so-called 'maintenance and reliever' strategy.[19-23] Two recently published studies have shown that anti-inflammatory reliever therapy with an ICS-LABA (budesonide-formoterol) combination, given on an as-needed basis in the absence of regular maintenance treatment, is efficacious for the treatment of mild asthma.[24,25] These important advances resulted in a major change to the GINA recommendations in 2019 for the management of mild asthma,[9,26] with as-needed ICS-formoterol becoming the preferred reliever option across all treatment steps.[9]

In the second half of 2018, specialists from across Italy met to discuss these topics at a series of specially convened meetings. During these meetings, participants critically reviewed the relevant literature and provided advice on practical aspects related to therapeutic approaches in mild asthma. The objective of this article is to present the emerging consensus from these meetings in light of the most recent data on this 'hot' topic.

2. LIMITATIONS OF CONVENTIONAL ASTHMA TREATMENT

During the previous major revision of the GINA guidelines in 2014, it was recognized that no evidence was available to support two important aspects of conventional asthma treatment: *i*) the symptom-based cut-off (i.e., symptoms on > 2 days per week) for initiating controller therapy with ICS, and *ii*) the long-term safety of treating step 1 asthma with SABA alone.[2] The former aspect was then reviewed in light of compelling evidence of the presence of airway inflammation in patients with mild asthma.[6-8] In addition, the underuse of ICS has been associated with increased risk of severe asthma exacerbations[27] and asthma death in these patients.[6] A number of studies have investigated and further supported the benefits of anti-inflammatory treatment in mild asthma.[28-32] A recent *post hoc* analysis of the Steroid Treatment As Regular Therapy (START) study showed that daily budesonide decreased the risk of severe asthma-related events, and improved lung function and symptom control in mild recent-onset asthma.[32]

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A major limitation of a treatment strategy based on the early introduction of regular controller therapy is poor adherence.[12,14,15,18] Indeed, a common pattern of inhaled medication use highlighted by a number of surveys [12,13] is the use of treatment only when symptoms occur, and avoidance of treatment when this is perceived as unnecessary. When symptoms worsen, patients show a preference for reliever therapies, which may result in the overuse of SABAs.[12,13] Indirect evidence suggests that the overuse of beta-agonists alone is associated with increased risk of asthma death.[33,34]

With regard to the safety of beta-agonists used alone, concerns have been raised for both SABAs and LABAs since their introduction into the asthma pharmacopeia.[34-40] Studies prompted by epidemics of asthma deaths in the 1960s and 1970s implicated beta-agonists in increased asthma mortality, and suggested that monotherapy with beta-agonists had a permissive effect on airway inflammation and hyper-responsiveness.[35,36] A recent European survey confirms that SABA overuse is common in Europe [41] and is associated with increased risks of exacerbations and asthma-related death.[42] A meta-analysis of 19 trials with a total of 33 826 participants published in 2006 found that LABA monotherapy increased the risk of exacerbations requiring hospitalization (odds ratio [OR], 2.6; 95% confidence interval [CI], 1.6 to 4.3) and life-threatening exacerbations (OR, 1.8; 95% CI, 1.1 to 2.9) compared with placebo.[37] In contrast, when beta-agonists are used in combination with ICS, the evidence concerning deleterious effects is less consistent.[23,35,40] Overall, the available data support the safety of therapies that combine beta-agonists with ICS.[23,35] As a consequence, SABAs and LABAs should not be used as controller monotherapy.[35,37-40]

A U. S. Food and Drug Administration (FDA) review of large clinical trials to evaluate the safety of adding LABAs to ICS for the treatment of asthma with different inhaled combinations (including fluticasone-salmeterol, mometasone-formoterol and budesonide-formoterol) determined that the use of ICS-LABA in fixed-dose combination does not result in a significant increase in the risk of serious asthma-related events compared to ICS alone.[43] In particular, a post-marketing study requested by the FDA,[44] in which 11 693 patients with asthma were randomized to either budesonide-formoterol or budesonide showed that the two treatment groups had a similar risk of serious asthma-related events.

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Notably, the risk of asthma exacerbations was 16.5% lower with budesonide-formoterol than with budesonide maintenance (Table 1).

International recommendations have long provided somewhat confusing advice about the use of beta-agonists, by stating that LABAs can only be used in combination with ICS, while SABAs are allowed as rescue monotherapy.[9,15] The upper limit of the number of total daily inhalations approved by regulatory authorities is 12 for budesonide-formoterol, although a total daily dose of more than eight inhalations is not normally needed.[45]

A survey conducted in Europe among 8000 asthma patients to evaluate patient perceptions of control and attitudes to asthma revealed that many patients regard their asthma as controlled and not serious, despite experiencing symptoms and exacerbations.[13] Misunderstanding of the term "asthma control" between physicians and patients may explain this observation.[15] Also, it should be noted that the rapid symptomatic relief provided by bronchodilators could mask insufficiently controlled asthma, leading to a misperception of asthma control.[15,46,47]

3. ALTERNATIVE TREATMENT APPROACH BASED ON AS-NEEDED ANTI-INFLAMMATORY RELIEVER THERAPY

The single-inhaler combination of an ICS with a rapid-onset bronchodilator taken on an as-needed basis has been regarded over the past decade as a potential strategy for overcoming the limitations of conventional approaches across all steps of asthma treatment.[15-18,48] By combining ICS with bronchodilators, each time a patient uses a rapid-acting beta-agonist for symptom relief they are simultaneously inhaling a dose of anti-inflammatory medication that targets the underlying airway inflammation.

4. EVIDENCE SUPPORTING THE ALTERNATIVE APPROACH

4.1 Moderate-severe asthma

The feasibility and validity of as-needed anti-inflammatory reliever therapy for the treatment of moderate-severe asthma is well established. A large body of evidence from large, mostly double-blind, randomized clinical trials is available for the combination budesonide-formoterol (Table 1).[19-23] A double-blind randomized study in 2760 patients tested the hypothesis that in patients receiving a low maintenance dose of budesonide-formoterol, the replacement of a SABA reliever with as-needed budesonide-formoterol would provide more

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appropriate anti-inflammatory therapy, thereby reducing exacerbations.[21] Budesonide-formoterol used for both maintenance and as-needed relief prolonged the time to first severe exacerbation, resulting in a 45–47% lower exacerbation risk versus the conventional strategy (budesonide-formoterol plus as-needed SABA, or budesonide plus as-needed SABA). A 12-month, double-blind study (SMILE) compared the efficacy and safety of three reliever strategies in 3394 symptomatic patients receiving budesonide-formoterol maintenance therapy: a traditional SABA (terbutaline); a rapid-onset LABA (formoterol); and a combination of LABA and ICS (budesonide-formoterol).[22] Time to first severe exacerbation (the primary endpoint) was significantly longer with as-needed budesonide-formoterol as reliever compared with as-needed formoterol, and with as-needed formoterol versus terbutaline. The findings of this study showed that the ICS component of as-needed budesonide-formoterol resulted in additional reductions in overall rates of severe exacerbations and emergency-room visits compared with as-needed formoterol alone.

The use of a combination of an ICS with a rapid-onset bronchodilator for maintenance and reliever treatment is also supported by the findings of a double-blind, randomized trial in 1714 patients with moderate-severe asthma from 14 European countries: maintenance plus as-needed beclomethasone-formoterol significantly increased the time to first exacerbation, and reduced the risk of exacerbations and the number of days with mild asthma exacerbations, compared with maintenance beclomethasone-formoterol plus as-needed salbutamol (albuterol).[49] A recent meta-analysis of 16 randomized trials, in a total of 22 524 adult patients with persistent asthma, has confirmed the efficacy of anti-inflammatory reliever therapy over conventional treatment in reducing the risk of asthma exacerbations (Table 1),[50] which constitutes one of the components (along with control of symptoms) of the GINA asthma management goals.[9] When referring to control of symptoms, the maintenance and reliever approach has provided similar or higher efficacy in achieving asthma control compared to the standard approach.[19,20,22,49] The efficacy of this strategy has also been documented with beclomethasone-formoterol used as rescue medication on top of regular treatment with the same combination,[49] with an upper limit of the number of total daily inhalations approved by regulatory authorities of eight.[51]

Thus, GINA now includes as-needed ICS-formoterol as preferred rescue medication at steps 3-5.[9]

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4.2 Mild asthma

A number of early studies examined the feasibility of the as-needed anti-inflammatory reliever approach in mild-moderate asthma (Table 2).[48,52,53] A 6-month study in 697 patients with mild-moderate asthma randomly assigned to single-inhaler budesonide-formoterol for maintenance therapy plus budesonide-formoterol for symptom relief, or higher dose budesonide plus as-needed SABA (terbutaline).[53] The primary efficacy variable was morning peak expiratory flow (PEF). Patients receiving budesonide-formoterol showed greater improvements in morning PEF than patients receiving budesonide plus as-needed terbutaline. The risk of having a severe exacerbation was 54% lower with budesonide-formoterol than with budesonide plus as-needed terbutaline. A 6-month study in 455 patients with mild persistent asthma tested the hypothesis that symptom-based, as-needed use of the combination ICS-SABA (salbutamol) would be as effective in providing symptom control as the ICS taken at the same dose twice daily plus as-needed SABA.[48] The study showed that as-needed ICS-salbutamol in the absence of regular maintenance treatment was as effective as regular beclomethasone, and superior to as-needed SABA alone, in improving lung function and reducing the number of exacerbations, with a lower cumulative dose of ICS. A study performed to compare strategies of ICS adjustment in 342 patients with mild-moderate asthma controlled by low-dose ICS confirmed the feasibility of symptom-based ICS treatment.[52] Three adjustment methods were assessed: symptom-based (patients were instructed to take ICS every time they took reliever therapy); based on physician assessment; and biomarker-based (fraction of exhaled nitric oxide). The rates of treatment failure and the rates of asthma exacerbation were overlapping among the three adjustment groups.

Two recent trials, SYGMA 1 and SYGMA 2, have further demonstrated that as-needed anti-inflammatory reliever therapy is also feasible in mild asthma (Table 2); in both studies, as-needed budesonide-formoterol was administered through a dry powder inhaler device.[24,25] SYGMA 1 was a 52-week, double-blind, randomized trial involving asthma patients eligible for GINA step 2 treatment.[25] Patients (n = 3849) were randomly assigned to one of three treatments: twice daily placebo plus as-needed terbutaline (terbutaline group); twice daily placebo plus as-needed budesonide-formoterol (budesonide-formoterol group); or twice daily budesonide plus as-needed terbutaline (budesonide maintenance group). The primary endpoint was asthma control, measured as the percentage of electronically recorded weeks with well-controlled asthma (based on use of as-needed medications, asthma symptom

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scores, night-time awakening, morning PEF, and additional use of inhaled or systemic corticosteroids). Secondary objectives included rates and time to severe exacerbation.
In terms of the primary endpoint, as-needed budesonide-formoterol was superior to as-needed terbutaline (OR, 1.14; 95% CI, 1.00 to 1.30; *P* = .046) and less effective than budesonide maintenance (OR, 0.64; 95% CI, 0.57 to 0.73). Budesonide-formoterol used as needed resulted in significant 60% and 64% reductions in moderate-severe and severe exacerbations, respectively, compared with terbutaline used as needed. No significant difference in the rate of moderate-severe and severe exacerbations in the budesonide-formoterol group in comparison to budesonide maintenance was observed. Of note, the median daily dose of ICS in the budesonide-formoterol group was only 17% of that in the budesonide maintenance group.
The 52-week, double-blind SYGMA 2 trial was designed in parallel with SYGMA 1 to investigate as-needed budesonide-formoterol in patients with mild asthma, in a more pragmatic setting than SYGMA 1 (i.e., patients did not receive daily reminders to use maintenance medication).[24] Patients (n = 4215) eligible for GINA step 2 treatment were randomly assigned to receive either twice-daily placebo plus as-needed budesonide-formoterol or twice-daily budesonide maintenance therapy plus as-needed terbutaline. The primary endpoint was the annualized rate of severe exacerbations. The study showed that as-needed budesonide-formoterol was non-inferior to budesonide maintenance therapy in terms of the annualized rate of severe asthma exacerbations, with rates of 0.11 (95% CI, 0.10 to 0.13) and 0.12 (95% CI, 0.10 to 0.14), respectively. There were no significant differences between groups in the time to first severe asthma exacerbation. The median daily dose of ICS was 75% lower in the budesonide-formoterol group than in the budesonide maintenance group. As also seen in the SYGMA 1 trial, improvements in secondary endpoints related to asthma control were greater with budesonide maintenance therapy than with as-needed budesonide-formoterol. However, the differences in these treatment outcomes were small and below the threshold of clinical relevance identified by the minimal clinically important differences.[24]

Evidence from pragmatic trials designed to reflect real-life clinical practice confirms findings from the SYGMA 1 and SYGMA 2 trials (Table 2).[54,55] For example, the open-label Novel START trial in patients with mild asthma randomized to one of three treatment groups: as-needed salbutamol, budesonide plus as-needed salbutamol (budesonide maintenance therapy), or as-needed budesonide-formoterol has shown that as-needed anti-inflammatory reliever

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therapy with budesonide-formoterol was superior to as-needed SABA and equivalent to budesonide maintenance therapy for the prevention of asthma exacerbations, but superior to budesonide maintenance therapy for the prevention of severe exacerbations.[54] The efficacy of as-needed budesonide-formoterol in patients with mild-moderate asthma was recently reported from a 52-week open-label, multicentre, randomized controlled trial (PRACTICAL). Interestingly, the absolute rate of severe exacerbations per patient per year was lower in the as-needed budesonide-formoterol group compared with the maintenance budesonide plus terbutaline as-needed group (0.119 vs 0.172; relative rate 0.69; 95% CI, 0.48–1.00; P = .049).[56] In addition, there is evidence for the efficacy of budesonide-formoterol when used as preventative medication in exercise-induced asthma.[57]

5. IMPLEMENTATION OF AS-NEEDED ANTI-INFLAMMATORY RELIEVER THERAPY IN CLINICAL PRACTICE

The as-needed anti-inflammatory reliever approach, based on the combination of an anti-inflammatory agent with a bronchodilator (e.g. formoterol), appears to be valid across all degrees of asthma severity, including mild asthma, and may constitute a feasible alternative to conventional treatment. The new approach may reduce patient over-reliance on SABA and reduce the risk of exacerbations. Given that patients with mild disease constitute the largest subgroup of the asthma population,[6] optimizing the approach to step 1–2 asthma is a major advance in the management of asthma. Additional practical benefits include the availability of single-inhaler formulations of anti-inflammatory reliever, improved consistency of treatment goals and continuity of treatment (switch from as-needed ICS-LABA in steps 1–2 to regular ICS-LABA plus as-needed ICS-LABA in steps 3–5) across the entire spectrum of asthma severity.

Based on the large body of evidence collected over the past decade, and on recent findings from the SYGMA trials, the 2020 updated GINA guidelines recommend that patients with step 1 asthma start controller treatment with as-needed ICS-formoterol, while treatment with a SABA alone is no longer recommended.[9] As-needed ICS-formoterol or daily regular low-dose ICS are the recommended controller options for step 2 asthma. Overall, as-needed ICS-formoterol is the preferred option for reliever therapy across all asthma steps.[9]

Accuracy in communication between physician and patient is crucial. Patients should be clearly informed about the importance of addressing symptoms not only with reliever

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medication, but also with anti-inflammatory medication. The relevance of exacerbation prevention should also be clearly explained. As patients with mild asthma usually refer to general practitioners, family doctors, and paediatricians, adequate education about the new strategy should also be provided to non-asthma specialists. In addition, the advantages of carrying one single inhaler to be used regularly and as a reliever medication over the inconveniences/difficulties in using two different devices (only one of which is to be carried as rescue), with the related increased risks of errors and mistakes in the use of inhalers, should be also taken into account and discussed.

The higher costs of single-inhaler ICS-LABA therapies relative to SABAs may constitute a barrier to the implementation of the new approach in clinical practice. At the same time, the reduced use of ICS achieved with as-needed budesonide-formoterol treatment is relevant to many patients, and may also have positive economic consequences.[56] Pharmacoeconomic analyses are required to assess the impact of the new treatment approach on costs.[58-61]

Unresolved issues concerning the implementation of as-needed anti-inflammatory reliever therapy in clinical practice include the identification of eligible patients, the adjustment of treatment (e.g. when to step up or down), the outcomes to be considered for the evaluation of the response to treatment and the impact of anti-inflammatory reliever therapy on the natural history of asthma and airway remodeling. There is also a need for studies of anti-inflammatory reliever in children, where the dependency on SABA was first established.

6. CONCLUSIONS

As-needed anti-inflammatory reliever therapy is emerging as a valuable new approach to the management of asthma for patients at GINA steps 1–2, and its now-established adoption in patients at steps 3–5 has been further consolidated in the latest version of the GINA guidelines.[9] This therapeutic strategy simplifies asthma management, improves safety and ensures continuity of care. It may also help overcome two long-standing limitations of conventional strategies, namely poor adherence to maintenance therapy with ICS and overuse of SABAs to control symptoms.

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Conflicts of interest

A.B. reports payments for advisory board membership, consultancy, payment for lectures, grants for research, and travel expenses reimbursement from Chiesi, AstraZeneca, GlaxoSmithKline, Novartis, Guidotti, Roche, and Menarini.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed.

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Appendix 1. List of the participants in the three regional meetings

Filippo Andò, University of Messina, Messina, Italy; **Leonardo Antonicelli**, University Hospital, Ancona, Italy; **Salvatore Battaglia**, University of Palermo, Palermo, Italy; **Bianca Beghé**, University of Modena and Reggio Emilia, Modena, Italy; **Fulvio Braido**, University of Genoa, Ospedale Policlinico IRCCS San Martino, Genoa, Italy; **Marco Caminati**, Verona University Hospital and University of Verona, Verona, Italy; **Maria Teresa Costantino**, ASST Mantova, Mantova, Italy; **Mariella D'Amato**, Federico II University and AO Monaldi Dei Colli Hospital, Naples, Italy; **Federico Dente**, University of Pisa, Pisa, Italy; **Danilo Di Bona**, University of Bari "Aldo Moro", Bari, Italy; **Nicola Facciolongo**, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy; **Alessandro Fois**, University of Sassari, Sassari, Italy; **Elda Graziani**, Policlinico "Umberto I", Rome, Italy; **Girolamo Pelaia**, University "Magna Græcia" of Catanzaro, Catanzaro, Italy**; Sergio Poto**, A.O.U. San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy; **Dejan Radovanovic**, University of Milan and Ospedale "L. Sacco", Milan, Italy; **Gabriele Rumi**, Università Cattolica del Sacro Cuore - Fondazione Policlinico "A. Gemelli" IRCCS, Rome, Italy; **Eleonora Savi**, Piacenza Hospital, Piacenza, Italy; **Pietro Schino**, Miulli General Hospital, Acquaviva delle Fonti (BA), Italy; **Paolo Solidoro**, Molinette Hospital, Città della Salute e della Scienza and University of Turin, Turin, Italy.

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Table 1. As-needed anti-inflammatory reliever therapy in patients with moderate-severe asthma

Reference	Study design	Treatments	Treatment duration	No. pts	Primary efficacy endpoint	Other efficacy endpoint
O'Byrne et al. 2005 [21]	R, DB, PG, MC	bud/form 80/4.5 µg bid + 80/4.5 µg as needed (bud/form maintenance + reliever) bud/form 80/4.5 µg bid + terb 0.4 mg as needed (bud/form + SABA) bud 320 µg bid + terb 0.4 mg as needed (bud + SABA)	12 mo	2760	Time to first severe asthma exacerbation significantly prolonged with bud/form maintenance + relief compared with bud/form + SABA and bud + SABA (both $P < .001$)	Exacerbation risk with bud/form maintenance + relief 45% lower vs bud/form + SABA (HR, 0.55; 95% CI, 0.44 to 0.67) and 47% lower vs bud + SABA (HR, 0.53; 95% CI, 0.43 to 0.65)
Rabe et al. 2006 [22] (SMILE)	R, DB, PG, MC	bud/form 160/4.5 µg bid + bud/form 160/4.5 µg as needed (bud/form maintenance + reliever)	12 mo	3394	Time to first severe exacerbation significantly prolonged with bud/form maintenance + relief vs bud/form + form ($P = .0048$) or terb ($P < .0001$)	As-needed bud/form reduced risk of severe exacerbation by 27% (95% CI, 10 to 41) vs form and by 45% (95% CI, 32 to 55) vs terb

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		bud/form 160/4.5 µg bid + form 4.5 µg as needed bud/form 160/4.5 µg bid + terb 0.4 mg as needed				
Bousquet et al. 2007 [19]	R, DB, PG, MC	bud/form 2 × 160/4.5 µg bid + bud/form 160/4.5 µg as needed (bud/form maintenance + reliever) salm/flut 50/500 mg bid + terb 0.4 mg as needed	6 mo	2309	Time to first exacerbation not significantly different between treatment groups (HR, 0.82; *P* = .12)	Overall exacerbation rate significantly lower with bud/form maintenance + relief vs salm/flut + terb (25 vs 31 events/100 pts/year, respectively; *P* = .039)
Kuna et al. 2007 [20]	R, DB, DD, PG,	bud/form 160/4.5 µg bid + as needed salm/flut 2 × 25/125 µg bid + terb as needed bud/form 320/9 µg bid	24 wk	3335	Time to first severe exacerbation significantly prolonged with bud/form MART vs salm/flut (*P* = .0034) and bud/form (*P* = .023)	Risk of first severe exacerbation reduced by 33% with bud/form MART vs salm/flut (HR, 0.67; 95% CI, 0.52 to 0.87; *P* = .003) and by 26% vs bud/form (HR, 0.74; 95% CI, 0.56 to 0.96; *P* =

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		+ terb as needed				.026)
Sears et al. 2008 [23]	R, OL, PG, MC	bud/form 160/4.5 µg bid + as needed CBP	26 wk	1538	Time to first severe asthma exacerbation was not significantly different between treatment groups (HR, 0.99; 95% CI, 0.70 to 1.41; *P* = .95)	Rate of severe asthma exacerbation was similar between treatment groups
Peters et al. 2016 [44]	R, DB, MC, post-marketing study	bud/form 2 × 80/4.5 µg bid or 2 × 160/4.5 µg bid bud 2 × 80 µg bid or 2 × 160 µg bid	26 wk	11 693	The risk of a first asthma exacerbation was 16.5% lower with bud/form vs bud (HR, 0.84; 95% CI, 0.74 to 0.94; *P* = .002), and was consistent for both doses of bud	Serious asthma-related events occurred in 43 pts and 40 pts receiving bud/form and bud, respectively Time to first serious asthma-related event demonstrated statistical non-inferiority between treatments (HR, 1.07; 95% CI, 0.70 to 1.65)
Sobieraj et al. 2018 [50]	Meta-analysis	bud/form maintenance + as needed vs ICS ± LABA as controller therapy and SABA as reliever therapy		22 524 (≥12 years)		bud/form maintenance + as needed was associated with a significantly reduced risk of asthma exacerbations vs the same dose of ICS + LABA as

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	controller therapy (RR, 0.68 [95% CI, 0.58 to 0.80]; absolute RD, −6.4% [95% CI, −10.2% to −2.6%]) and vs a higher dose of ICS + LABA as controller therapy (RR, 0.77 [95% CI, 0.60 to 0.98]; absolute RD, −2.7% [95% CI, −5.2% to −0.3%])

Abbreviations: beclo, beclomethasone; bid, twice a day; bud, budesonide; CBP, conventional best practice; CI, confidence interval; DB, double-blind; DD, double-dummy; flut, fluticasone; form, formoterol; HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; MART, maintenance and reliever therapy; MC, multicentre; mo, month; OL, open-label; R, randomized; PG, parallel-group; pts, patients; RD, risk difference; RR, risk ratio; SABA, short-acting beta-agonist; salm, salmeterol; terb, terbutaline; vs, versus; wk, week.

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Table 2. As-needed anti-inflammatory reliever therapy in patients with mild-moderate or mild asthma

Reference	Study design	Treatments	Treatment duration	No. pts	Primary efficacy endpoint	Other efficacy endpoint
Mild-moderate asthma						
Rabe et al. 2006 [53]	R, DB, PG, AC, MC	bud/form 2 × 80/4.5 µg od in the evening + bud/form as needed (bud/form maintenance + reliever) bud 2 × 160 µg od in the evening + terb 0.4 mg as needed	6 mo	697	Greater improvement from baseline in morning PEF in pts receiving bud/form maintenance + relief vs bud (34.5 L/min vs 9.5 L/min, respectively; $P < .001$)	54% lower risk of having a severe exacerbation with bud/form maintenance + relief vs bud ($P < .01$)
Mild asthma						
Calhoun et al. 2012 [52] (BASALT)	R, P, 3-group, PC, MB	SBA (beclomethasone, when rescue salb was used) PABA (beclomethasone adjustment dosing based on National Heart, Lung, and Blood Institute guidelines) BBA (beclomethasone adjustment dosing based on	9 mo	342	Time to first treatment failure not significantly different between treatment strategies	9-month Kaplan-Meier failure rates were 22%, 20%, and 15% for PABA, BBA, and SBA, respectively

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		exhaled nitric oxide values)				
Papi et al. 2013 [49]	R, DB, MC	beclo/form 100/6 µg bid + as needed vs beclo/form 100/6 µg bid + as needed SABA	48 wk	1714	Time to first severe asthma exacerbation significantly prolonged with beclo/form bid + as needed (*P* = .0003); 36% reduction in risk (HR 0.64, 95% CI, 0.49-0.82)	Number of days with mild asthma exacerbation lower with beclo/form bid + as needed (*P* = .021)
O'Byrne et al. 2018 [25] (SYGMA 1)	R, DB, PG, MC	plc bid + terb 0.5 mg as needed (as-needed terb) plc bid + bud/form 200/6 µg as needed (as-needed bud/form) bud 200 µg bid + terb 0.5 mg as needed (bud maintenance therapy)	52 wk	3849	As-needed bud/form was superior to as-needed terb in terms of the mean percentage of weeks with well-controlled asthma per patient (34.4% vs 31.1% of weeks; OR, 1.14; 95% CI, 1.00 to 1.30; *P* = .046)	as-needed bud/form was inferior to bud maintenance therapy in terms of the mean percentage of weeks with well-controlled asthma per patient (34.4% vs 44.4%; OR, 0.64; 95% CI, 0.57 to 0.73) The rate of severe exacerbations was 64% lower with as-needed bud/form vs as-needed terb, but was not significantly different between as-needed bud/form and bud maintenance therapy
Bateman et al. 2018 [24]	R, DB, PG,	plc bid + bud/form 200/6 µg as needed (as-needed	52 wk	4215	As-needed bud/form was non-inferior to bud maintenance	The total number of severe exacerbations (217 vs 221 for

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(SYGMA 2)	MC	bud/form) bud 200 µg bid + terb 0.5 mg as needed (bud maintenance therapy)			therapy in terms of the annualized rate of severe exacerbations (0.11 [95% CI, 0.10 to 0.13] and 0.12 [95% CI, 0.10 to 0.14], respectively). The RR between groups = 0.97 (one-sided 95% upper confidence limit, 1.16)	as-needed bud/form vs bud maintenance therapy) and the time to the first severe asthma exacerbation (HR, 0.96; 95% CI, 0.78 to 1.17) were similar between treatment groups
Beasley et al. 2019 [54] (Novel START)	R, OL, PG, MC	2 × salb 100 µg as needed (salb group) bud 200 µg bid + 2 × salb 100 µg as needed (bud maintenance group) bud/form 200/6 µg as needed (bud/form group)	52 wk	668	The annualized rate of asthma exacerbations per patient was lower in the bud/form group vs the salb group (0.195 vs 0.400; relative rate, 0.49; 95% CI, 0.33 to 0.72; $P < .001$), but was not significantly different from that in the bud maintenance group (0.195 vs 0.175; relative rate, 1.12; 95% CI, 0.70 to 1.79; $P = 0.65$)	There were fewer severe exacerbations in the bud/form group vs the salb group and bud maintenance group (9 vs 23 and 21, respectively)

Abbreviations: AC, active-controlled; BASALT, Best Adjustment Strategy for Asthma in the Long Term; BBA, biomarker-based adjustment; beclo, beclomethasone; BEST, Beclomethasone plus Salbutamol Treatment; bid, twice a day; bud, budesonide; CI, confidence interval; DB,

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double-blind; DD, double-dummy; form, formoterol; ICS, inhaled corticosteroids; MB, multiply-blinded; MC, multicentre; mo, month; od, once daily; OL, open-label; OR, odds ratio; PEF, peak expiratory flow; P, parallel; PABA, physician assessment–based adjustment; PG, parallel-group; plc, placebo; pts, patients; R, randomized; RR, rate ratio; salb, salbutamol (albuterol); SBA, symptom-based adjustment; terb, terbutaline; vs, versus; wk, week.

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