EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Series

The Management of Mild Asthma

Paul M. O'Byrne, Helen K. Reddel, Richard Beasley

Please cite this article as: O'Byrne PM, Reddel HK, Beasley R. The Management of Mild Asthma. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.03051-2020).

REVISED: Clean Version

The Management of Mild Asthma

Paul M O'Byrne[1], Helen K Reddel[2], Richard Beasley[3]

[1] Firestone Institute for Respiratory Health, St. Joseph's Hospital and Department of Medicine, McMaster University, Hamilton, Ontario, Canada. [2] Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia. [3] Medical Research Institute of New Zealand, Newtown, Wellington 6242, New Zealand and Capital and Coast District Health Board, Wellington, New Zealand.

Corresponding Author: Dr Paul M O'Byrne, McMaster University Medical Centre, 2E1, 1280 Main St West, Hamilton, Ontario, Canada, L8S 4LA.

Email: obyrnep@mcmaster.ca

Word Count: Abstract: 245

Manuscript: 3240

References: 57

Keywords: asthma management, adherence, inhaled corticosteroid/long acting beta 2-agonist

ABSTRACT

Inhaled corticosteroids (ICS) have been recommended as a maintenance treatment, either alone or together with long-acting inhaled β_2-agonists, for all asthma patients. Short acting β_2-agonists (SABA) are rapid onset bronchodilators, which provide symptom relief, but have no anti-inflammatory properties, yet are the most widely used as-needed reliever treatment for asthma, and often the only treatment prescribed. Asthma patients can find adhering to daily preventative medication with ICS difficult and will often revert to using as-needed SABA as their only treatment, increasing their risk of exacerbations. The purpose of this review was to evaluate the efficacy of reliever medications that contain an ICS when compared to SABA as a reliever, or to maintenance ICS and SABA as reliever, in mild asthma patients.

Nine studies were identified which have evaluated the use of ICS as a component of an as-needed reliever in patients with mild asthma. Four of the most recent studies compared the combination of ICS/formoterol to SABA as reliever.

An ICS containing reliever medication was superior to SABA as reliever alone, and was equivalent to maintenance ICS and SABA as reliever, particularly in reducing risks of severe asthma exacerbations, in studies which compared these reliever options.

SABAs should not be used as a reliever without ICS. The concern about patients with mild asthma not being adherent to maintenance ICS, supports a recommendation that ICS/formoterol should be considered as a treatment option instead of maintenance ICS, to avoid the risk of patients reverting to SABA alone.

Identifying Mild Asthma

Asthma is a common disease with a worldwide prevalence of more than 340 million. It is characterized by airway inflammation and variable airflow obstruction, associated with symptoms of wheeze, cough, shortness of breath, and chest tightness.

As with many chronic diseases, asthma was traditionally classified by severity into mild, moderate or severe disease. This classification was based on symptom frequency, degree of airflow obstruction, and number and frequency of asthma exacerbations, and was used to provide treatment recommendations. The earliest iteration of the Global Initiative for Asthma (GINA) strategy document in 1995 stated that "descriptions of asthma severity are useful because asthma therapy has a stepwise approach in which the level of therapy is increased as the severity of the asthma increases" [1]. However, in a seminal paper, published in 1996, Cockcroft [2] argued that asthma severity and asthma control were inextricably linked. Thus, asthma severity can only be established retrospectively after the minimal treatment requirement to achieve asthma control is known. This approach was adopted in subsequent iterations of the GINA strategy document [3] and other national asthma guidelines [4], and was recommended by an American Thoracic Society/European Respiratory Society Task Force on asthma control, severity and exacerbations [5,6]. As a consequence of this approach, mild asthma is currently identified for clinical practice as a patient with well controlled asthma, manifest by infrequent symptoms (twice or less per week), no nocturnal awakenings, and normal activities of daily living, while treated with as-needed controller medication alone, or low-dose maintenance inhaled corticosteroids (ICS), or leukotriene receptor antagonists[7]. In the case of clinical trials in mild asthma, most studies have included

patients who would have been eligible for treatment with maintenance ICS or leukotriene receptor antagonists according to then-current guidelines.

Treatment Options for Mild Asthma

Inhaled adrenergic agonists were initially used to treat asthma as early as the 1930's[8]. Short acting β_2-agonists (SABA) were the first inhaled therapy to be developed for common use in asthma[9]. These are rapid onset bronchodilators, selective for the β_2-receptor, and which provide symptom relief, but have no anti-inflammatory properties. Subsequently, ICS were introduced as maintenance treatment for asthma[10], being very effective in reducing eosinophilic airway inflammation[11], improving airway hyperresponsiveness[12], asthma control[13] and reducing asthma exacerbation risk [14]. However, it is reported that, at least initially, general practitioners were reluctant to prescribe ICS because of fear of the severe side-effects that had been seen with systemic corticosteroids [15].

These two classes of drugs remain the most commonly prescribed treatments for asthma. Until recently, the way in which they were prescribed did not closely align with the evidence base for their efficacy and safety [16]. Although it was known that asthma is an airway inflammatory disorder, even in the mildest patients [17,18], for many years the recommendation in asthma treatment guidelines for first line treatment for mild disease was a SABA, which has no anti-inflammatory properties. This recommendation was based on the belief that if asthma is mild enough to only warrant 'occasional' short acting bronchodilator, the utility of recommending regular ICS seemed disproportionate and unnecessary. Another class of medication approved for the treatment of mild

asthma was leukotriene receptor antagonists (LTRAs) [19]. However, studies comparing the efficacy of LTRAs to low dose maintenance ICS have demonstrated the superiority of ICS in mild asthma patients previously taking SABA alone, particularly for reduction in severe exacerbations[20 21]. From 2014, finding a lack of evidence to support SABA-only treatment, GINA recommended maintenance ICS for patients with symptoms more than twice a month or with any risk factors for asthma exacerbations [22], a position that was supported by findings from the START study [23]; however, most guidelines continue to limit ICS to patients with symptoms more than twice a week.

From a patient's perspective, the most tangible measure of asthma control is day-to-day symptoms, which vary with time. Fast and effective symptom relief is a priority for patients. In mild asthma, when symptoms are not present, patients can find adhering to daily preventative medication with ICS difficult without any obvious immediate improvement that might provide a rationale for their use, and reluctance due to potential side effects. In contrast, because treatment with SABA is so effective during acute attacks, it may appear logical to patients for this to also be beneficial for the control of chronic asthma.

For several decades, it has been recognized that overuse of SABAs is associated with increased risk of asthma mortality[24], a finding unfortunately confirmed by the National Review of Asthma Deaths in the UK which demonstrated increased use of SABA and lack of ICS use associated with increased mortality[25]. These concerns have been supported by mechanistic studies showing regular use of SABA, for a little as one week, is associated with increased exercise bronchoconstriction[26] and allergic airway inflammation[27], and by studies showing that dispensing of ≥3 SABA canisters a year

(usage ≥3-4 times/week) is associated with increased asthma exacerbations[28] and all-cause mortality[29].

Low dose maintenance ICS has been extensively evaluated as a treatment option for mild asthma. These studies have demonstrated that low dose (even once daily) ICS was superior to SABA as needed as the only treatment in reducing asthma exacerbation risk[30,23], and this benefit persisted even when patients with very infrequent symptoms (0-1 days/week) were evaluated[31].

A major challenge with recommending the use of maintenance ICS for patients with mild asthma is adherence to the treatment. There is a very consistent body of evidence which shows that adherence to maintenance treatment in asthma is problematic, with many studies indicating that patients take less than 50% of recommended doses of maintenance treatment, which can be improved with a strategy of providing electronic inhaler reminders[32]. Adherence to maintenance treatment also decreases with time, and can be as low as 10-15% of patients refilling prescriptions for maintenance inhaled treatments, over a 1 year time frame [33].

ICS/LABA maintenance and reliever therapy

The long acting β_2 agonists (LABA) salmeterol, and the fast acting formoterol were developed in the 1990s. Initial studies were conducted to determine both safety and efficacy, particularly in combination with inhaled steroids (ICS/LABA) [34 35]. In patients receiving maintenance ICS therapy, clinical effectiveness was demonstrated by reducing severe exacerbations with ICS/LABA compared with ICS alone [36]. By contrast, in patients considered to have mild asthma not treated with maintenance ICS, adding

formoterol to ICS as part of maintenance treatment did not provide any additional benefit when compared to maintenance ICS alone[30]. However, formoterol for symptom relief reduced severe exacerbations, both with [36] [37] and without [38] maintenance ICS, compared with as-needed SABA.

In a real world setting, where LABAs were being used as the only treatment or not in combination with ICS, asthma related mortality was increased [39]. This led to the recommendation that LABAs be only used together with an ICS (ideally from the same device) in moderate and severe asthma [40], but despite these justifiable concerns about the use of LABA as a monotherapy in asthma, SABA monotherapy remained as the first line treatment option for patients with mild asthma.

For patients with moderate to severe asthma, maintenance treatment with ICS/LABA combinations has become the standard of care. In addition, the use of a combination ICS/ rapid onset LABA (formoterol) inhaler as both a maintenance and reliever therapy has been demonstrated to be superior to fixed dose ICS or combination ICS/LABA with SABA as reliever. This approach demonstrated a 25% to 40% relative risk reduction in severe exacerbation risk compared with fixed dose regimens in patients with a history of severe exacerbations[41]. This set a precedent of a patient centered approach in moderate to severe asthma, where patients have autonomy and control over escalating and de-escalating additional ICS/formoterol use based on current day-to-day symptoms. The rationale was that the fast-acting bronchodilator formoterol improves symptoms, but at the same time the underlying worsening inflammation is addressed with up-titration of treatment with ICS; however, both the ICS and the formoterol in the reliever inhaler contribute to the reduction in exacerbations [42].

ICS/SABA therapy as a reliever in mild asthma

The hypothesis that using a reliever that contained both a rapid onset β_2-agonist and an ICS would be superior to a β_2-agonist only as a reliever, was initially evaluated in 2007 in patients considered, at that time, to have mild asthma [43] (Table1). The BEST study consisted of four treatment arms, after a run-in period on moderate dose ICS: as needed combination ICS (beclometasone) and SABA (salbutamol) from a single inhaler; as needed SABA only; maintenance ICS with SABA as needed; and maintenance combination ICS/SABA with SABA as needed. The study demonstrated that symptom driven use of as needed combination ICS/SABA improved peak flow rates and the forced expired volume in one second (FEV_1) and reduced exacerbations, compared with as needed SABA alone, but was not different to the maintenance ICS and maintenance combination ICS/SABA group. The cumulative dose of ICS was, however, substantially lower in the as needed ICS/SABA group when compared to the other two ICS containing treatment arms.

In the TREXA study, in children aged 5-18 years with mild asthma (Table 1), using similar design and intervention arms, but with the ICS and SABA delivered from separate inhalers, Martinez *et al* [44] showed that treatment with maintenance low dose ICS reduced asthma exacerbations risk by 50% compared with SABA as needed alone. Treatment with ICS/SABA as needed also reduced the risk of exacerbations by almost 40%, but this did not reach statistical significance. Importantly, the use of maintenance ICS was associated with a 1.1cm decline in linear growth over 1 year, which was not seen with as needed ICS/SABA, because of the lower cumulative dose of ICS in this group.

The Best Adjustment Strategy for Asthma in the Long Term (BASALT) study in adults with well or partly controlled asthma on ICS therapy used a similar model of patients adjusting ICS use according to their requirement for SABA, again with separate inhalers[45]. The symptom-driven approach of instructing patients to take two actuations of their low dose beclomethasone (ICS) inhaler every time they took a SABA was at least as effective in terms of the time to treatment failure, compared with a 'gold standard' physician-based strategy of six-weekly adjustment of maintenance ICS dose, or a novel biomarker ICS-adjusted strategy.

A recent pragmatic study in African-American children and adolescents with well-controlled asthma on low dose ICS, LTRA or ICS/LABA randomised patients to symptom-based treatment with ICS taken whenever SABA was taken, or to guidelines-based adjustment of treatment by primary care providers. Asthma outcomes were similar between groups, with average ICS dose in the symptom-based treatment arm 26% of that with physician-adjusted treatment[46] (Table 1).

ICS/LABA combination therapy as a reliever in mild asthma

Based on the evidence that budesonide/formoterol (Bud/Form) as a reliever treatment reduces severe exacerbation risk compared with a SABA in patients with moderate to severe asthma on maintenance ICS/LABA (later summarized in a meta-analysis)[47], led to investigation of the use of Bud/Form (Symbicort) as needed in mild asthma (Table 1). The SYmbicort Given as needed in Mild Asthma (SYGMA) 1 Study was a randomized double blind, 52-week, 3 way parallel-group study of 3849 patients. The study evaluated the efficacy and safety of Bud/Form used as needed, compared to the SABA, terbutaline as needed, and to budesonide (200mcg) twice daily plus terbutaline as

needed. Patients were eligible if they needed maintenance low dose ICS treatment (GINA 2012 Step 2, including use of SABA on ≥3 days in the week before randomization)[48].

The primary efficacy results showed that Bud/Form as needed was superior to terbutaline as needed at reducing the number of well-controlled asthma weeks (based on a old definition of asthma control), but was inferior to maintenance budesonide[49]. Secondary outcomes demonstrated that Bud/Form as needed resulted in a 64% lower rate of severe exacerbations, and a 60% lower rate of moderate to severe exacerbations compared with terbutaline as needed, and prolonged the time to first severe exacerbation and the time to first use of additional corticosteroids for asthma. The Bud/Form as needed group also had a small, but significant, improvement in ACQ-5 score and a higher FEV_1 than the terbutaline as needed group. When compared with maintenance budesonide, there was no difference in the exacerbation outcomes, but these were achieved with an 83% lower ICS dose with Bud/Form as needed. However, maintenance budesonide also had a small, but significant, improvement in ACQ-5 score and a higher FEV_1 than the Bud/Form as needed group. These differences did not achieve levels considered to be clinically important. Importantly, with twice-daily inhaler reminders, adherence to the maintenance treatments in all three study arms was almost 80%. The median use of a reliever in this study was about 1 inhalation every 3 days, and while this had a wide distribution, on less than 0.5% of days in the study were >4 inhalations of as needed Bud/Form used.

The SYGMA 2 study (Table 1) randomly assigned 4215 patients who met the same entry criteria as SYGMA 1, but the study did not include electronic diaries or adherence

reminders and had less oversight from clinical research teams at the recruiting centers, to mimic a more real-world clinical setting[50]. Subjects were randomized to receive either 52 weeks of Bud/Form as needed compared to twice-daily maintenance budesonide with terbutaline as needed. The primary outcome in this study was the annual rate of severe exacerbations. For this outcome, Bud/Form as needed was non-inferior to maintenance budesonide, but with a 75% lower median daily ICS dose in the Bud/Form group. There was no difference between groups in the number of severe exacerbations that led to hospitalization or emergency room visits, or in the time to first severe asthma exacerbations. Similar to the SYGMA 1 study, maintenance budesonide had a small, but significant, improvement in ACQ-5 score and a higher FEV_1 than the Bud/Form as needed group. The adherence to maintenance treatment in the two study arms was 64%.

A third, more pragmatic study (Novel START)(Table 1), was a randomized, open label, parallel three-way group trial in 675 patients treated with the SABA salbutamol as needed, maintenance budesonide plus salbutamol as needed, or Bud/Form as needed[51]. Patients were eligible if they used SABA as their only asthma therapy in the 3 months prior to their inclusion, and by including patients with baseline SABA use as infrequent as twice a month, extended the evidence of efficacy to patients with infrequent symptoms; overall, 54% of patients had used SABA twice a week or less in the previous 4 weeks. The primary efficacy outcome was the annualized asthma exacerbation rate, which was 51% lower in the Bud/Form as needed group when compared to the salbutamol as needed group, but was not different to the maintenance budesonide group. Interestingly, in contrast to the SYGMA studies, the number of

severe exacerbations, although small, was significantly lower in the Bud/Form as needed group, when compared with both the salbutamol as needed and the maintenance budesonide groups. However, maintenance budesonide demonstrated the greatest improvements in in ACQ-5 scores, albeit the differences were small and again did not meet the minimally clinical important difference. There was no significant difference in FEV_1 across all time points between the 3 groups. Both of the ICS containing arms of the study significantly reduced the fraction of exhaled nitric oxide (F_ENO), when compared to the SABA treatment arm. The geometric mean F_ENO in the Bud/Form treatment arm was slightly higher than in the maintenance budesonide group, but the difference was small and of no clinical importance. These results demonstrate that Bud/Form has anti-inflammatory activity when administered by an as-needed reliever regimen in mild asthma, and do not support any concern that its use in this way will allow eosinophilic airway inflammation to progressively worsen; however, further long term studies need to be done to confirm this. Of interest, in this study, patients with mild asthma with elevated baseline blood eosinophils (>0.3 vs <0.15 x 109/L) had a higher risk of experiencing a severe asthma exacerbation[52], and the benefits of maintenance inhaled budesonide compared with salbutamol were greater in patients with high blood eosinophil counts. However, importantly, effects of Bud/Form as-needed on exacerbations and symptom control were independent of blood eosinophil or F_ENO biomarker profiles. This indicates that the efficacy of Bud/Form is generalizable to all patients with mild asthma, without need for inflammatory phenotyping. This differs from more severe asthma, where biomarker assessment may be helpful in titrating maintenance ICS dose [53].

The Novel START study was followed by another open label study (PRACTICAL)[54], enrolling 890 patients requiring or eligible for GINA step 2 treatments (Table 1). The study had two treatment arms; Bud/Form as needed or maintenance budesonide with terbutaline as needed. The results were very similar to Novel START, with a 31% reduction in the rate of severe asthma exacerbations with Bud/Form as needed, and an increase in the time to first exacerbation, compared with maintenance budesonide. Also, as in Novel START, the benefit with this regimen for risk reduction and asthma control in PRACTICAL was independent of baseline characteristics, including inflammatory markers such as blood eosinophils and FeNO, Another important clinical finding from the PRACTICAL study was that 90% of patients who were randomised to Bud/Form reported a preference for this regimen rather than maintenance ICS and SABA at the end of the trial.[55]

Finally, a study by Lazarinis et al[56] provided evidence that as-needed budesonide-formoterol taken for symptom relief and before exercise reduced the risk of exercise-induced bronchoconstriction to the same extent as 6 weeks of maintenance ICS, indicating that patients do not need to be given a SABA inhaler for pre-exercise use.

CONCLUSIONS

The studies comparing reliever medications which contain an ICS to using SABA alone, in patients with mild asthma, have put to rest the question of the optimal reliever treatment for these patients. In studies spanning childhood, adolescence and adults, an ICS containing reliever medication was superior to SABA reliever alone in almost every domain (Figure 1). For this reason, the GINA treatment algorithm now recommends that SABAs should not be used alone as sole therapy without ICS, and that combination

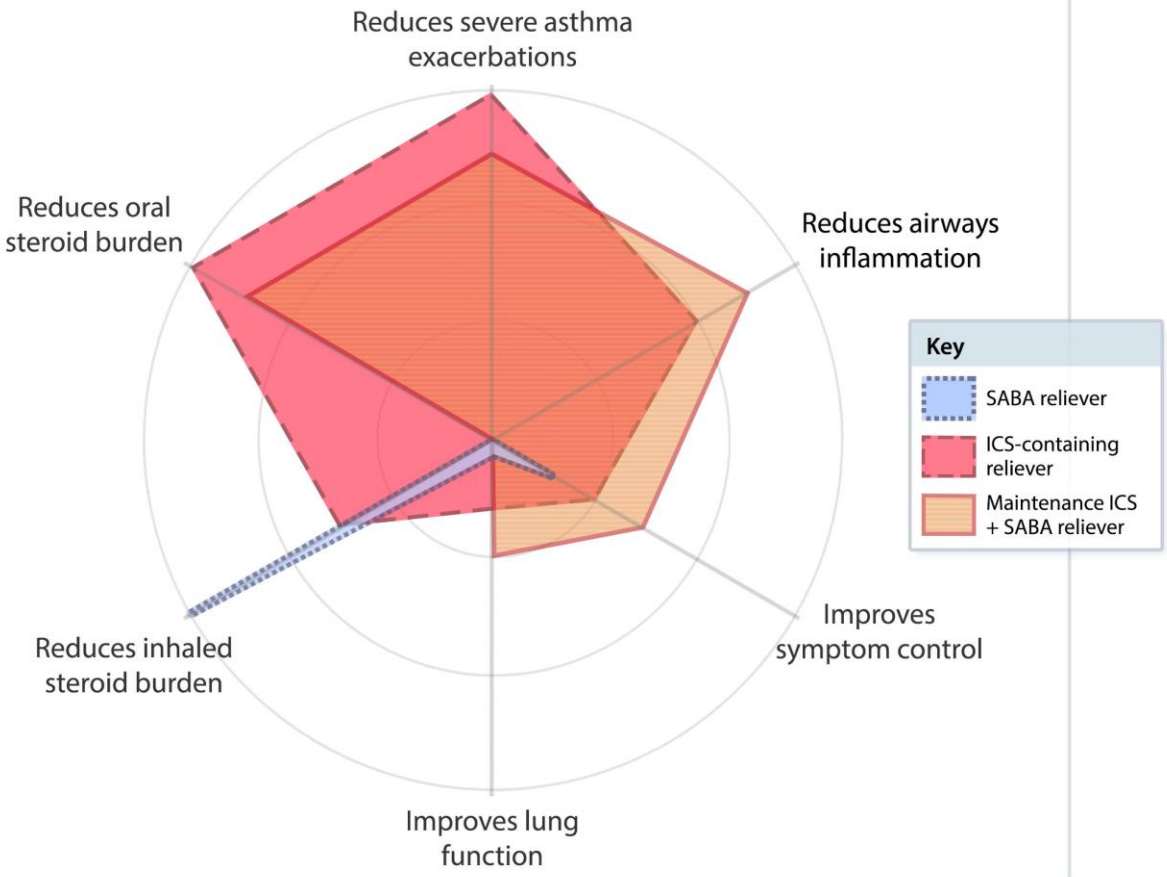
ICS-formoterol is preferred to SABA as reliever therapy in adults and adolescents[7]; however, there is no evidence for the safety of using ICS-formoterol as reliever for patients taking other ICS-LABA combinations. In addition, while maintenance ICS treatment for mild asthma is superior for some clinical outcomes, the concerns about many patients with mild asthma not being adherent to maintenance ICS, resulted in the GINA treatment algorithm recommending ICS-Form as an alternative to maintenance ICS, to avoid the risk of patients reverting to SABA alone.

Acknowledgements: The authors gratefully acknowledge the support of Dr Ciléin Kearns in designing the conceptual figure.

Figure Legend

Conceptual comparison of the relative benefit of the three treatment regimens for asthma: short-acting beta-agonist (SABA) reliever (blue area with dotted line); combination inhaled corticosteroid (ICS)/fast-onset beta-agonist reliever (red area with dashed line); maintenance ICS plus SABA reliever (brown area with solid line). The relative performance of each regimen is presented across six domains: reduction in severe exacerbations; reduction in airways inflammation; improvement in symptom control; improvement in lung function; reduction in ICS burden; reduction in oral corticosteroid burden. The relative performance of each regimen for each domain is based on the literature referenced in this Review. The greater the distance of each point from the axes centre, the better the performance in that domain.

Conceptual comparison of relative asthma treatment performance



REFERENCES:

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NHLBI/WHO Workshop Report. National Institutes of Health National Heart, Lung, and Blood Institute 1995.
2. Cockcroft DW, Swystun VA. Asthma control versus asthma severity. J Allergy Clin Immunol 1996;98:1016-8.
3. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008;31:143-78.
4. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007;120:S94-138.
5. Taylor DR, Bateman ED, Boulet LP, et al. A new perspective on concepts of asthma severity and control. Eur Respir J 2008;32:545-54.
6. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
7. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention. 2020:www.ginasthma.org.
8. Graeser JBR, A.H. Inhalation of adrenaline for the relief of asthma. Cal West Med 1935;43:110.
9. Tattersfield AE. Current issues with β 2-adrenoceptor agonists. Clinical reviews in allergy & immunology 2006;31:107-17.
10. Brown HM, Storey G, George WH. Beclomethasone dipropionate: a new steroid aerosol for the treatment of allergic asthma. Br Med J 1972;1:585-90.
11. Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a beta 2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. J Allergy Clin Immunol 1992;90:32-42.
12. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. Am Rev Respir Dis 1990;142:832-6.
13. O'Byrne PM, Naya IP, Kallen A, Postma DS, Barnes PJ. Increasing Doses of Inhaled Corticosteroids Compared to Adding Long-Acting Inhaled **B**2-Agonists in Achieving Asthma Control. Chest 2008;134:1192-9.
14. Haahtela T, Jarvinen M, Kava T, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med 1991;325:388-92.
15. Crompton G. A brief history of inhaled asthma therapy over the last fifty years. Prim Care Respir J 2006;15:326-31.
16. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? Eur Respir J 2017;50.
17. Kirby JG, Hargreave FE, Gleich GJ, O'Byrne PM. Bronchoalveolar cell profiles of asthmatic and nonasthmatic subjects. Am Rev Respir Dis 1987;136:379-83.
18. Beasley R, Roche WR, Roberts JA, Holgate ST. Cellular events in the bronchi in mild asthma and after bronchial provocation. Am Rev Respir Dis 1989;139:806-17.
19. Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. N Engl J Med 1999;340:197-206.
20. Bleecker ER, Welch MJ, Weinstein SF, et al. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. J Allergy Clin Immunol 2000;105:1123-9.

21. Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. J Allergy Clin Immunol 2001;107:461-8.
22. Reddel HK, Bateman ED, Becker A, et al. A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J 2015;46:622-39.
23. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003;361:1071-6.
24. Spitzer WO, Suissa S, Ernst P, et al. The use of beta-agonists and the risk of death and near death from asthma. N Engl J Med 1992;326:501-6.
25. Levy M, Andrews R, Buckingham R, et al. Why asthma still kills: the National Review of Asthma Deaths (NRAD): Royal College of Physcians; 2014.
26. Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. Am J Respir Crit Care Med 1996;153:65-9.
27. Gauvreau GM, Jordana M, Watson RM, Cockroft DW, O'Byrne PM. Effect of regular inhaled albuterol on allergen-induced late responses and sputum eosinophils in asthmatic subjects. Am J Respir Crit Care Med 1997;156:1738-45.
28. Stanford RH, Shah MB, D'Souza AO, Dhamane AD, Schatz M. Short-acting beta-agonist use and its ability to predict future asthma-related outcomes. Ann Allergy Asthma Immunol 2012;109:403-7.
29. Nwaru BI, Ekstrom M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting beta2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J 2020;55.
30. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med 2001;164:1392-7.
31. Reddel HK, Busse WW, Pedersen S, et al. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet 2017;389:157-66.
32. Foster JM, Usherwood T, Smith L, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. J Allergy Clin Immunol 2014;134:1260-8 e3.
33. Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. J Allergy Clin Immunol 2006;118:899-904.
34. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994;344:219-24.
35. Pearlman DS, Chervinsky P, LaForce C, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. N Engl J Med 1992;327:1420-5.
36. Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med 1997;337:1405-11.
37. Tattersfield AE, Lofdahl CG, Postma DS, et al. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. Lancet 2001;357:257-61.
38. Pauwels RA, Sears MR, Campbell M, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. Eur Respir J 2003;22:787-94.
39. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15-26.
40. Busse WW, Bateman ED, Caplan AL, et al. Combined Analysis of Asthma Safety Trials of Long-Acting beta2-Agonists. N Engl J Med 2018;378:2497-505.

41. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of Inhaled Corticosteroids and Long-Acting beta-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. JAMA 2018;319:1485-96.
42. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006;368:744-53.
43. Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med 2007;356:2040-52.
44. Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. Lancet 2011;377:650-7.
45. Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. JAMA 2012;308:987-97.
46. Sumino K, Bacharier LB, Taylor J, et al. A Pragmatic Trial of Symptom-Based Inhaled Corticosteroid Use in African-American Children with Mild Asthma. J Allergy Clin Immunol Pract 2020;8:176-85 e2.
47. Edwards SJ, von Maltzahn R, Naya IP, Harrison T. Budesonide/formoterol for maintenance and reliever therapy of asthma: a meta analysis of randomised controlled trials. Int J Clin Pract 2010;64:619-27.
48. O'Byrne PM, FitzGerald JM, Zhong N, et al. The SYGMA programme of phase 3 trials to evaluate the efficacy and safety of budesonide/formoterol given 'as needed' in mild asthma: study protocols for two randomised controlled trials. Trials 2017;18:12.
49. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med 2018;378:1865-76.
50. Bateman ED, Reddel HK, O'Byrne PM, et al. As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. N Engl J Med 2018;378:1877-87.
51. Beasley R, Holliday M, Reddel HK, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. N Engl J Med 2019;380:2020-30.
52. Pavord ID, Holliday M, Reddel HK, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. Lancet Respir Med 2020;8:671-80.
53. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002;360:1715-21.
54. Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet 2019;394:919-28.
55. Baggott C, Reddel HK, Hardy J, et al. Patient preferences for symptom-driven or regular preventer treatment in mild to moderate asthma: findings from the PRACTICAL study, a randomised clinical trial. Eur Respir J 2020;55.
56. Lazarinis N, Jorgensen L, Ekstrom T, et al. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. Thorax 2014;69:130-6.

TABLE 1: Studies in mild asthma with inhaled steroids in combination with rapid-onset β_2-agonists as needed.

Study Name (Ref #)	Patient Number	Age	Design	Duration	Treatment groups	Primary Outcome	Secondary Outcomes
SYGMA 1 (49)	3836	≥12 years	Phase 3, placebo controlled, double blind, randomized parallel group	52 weeks	1. Placebo bid with Bud/Form as needed 2. Placebo bid with terbutaline as needed 3. Bud bid with terbutaline as needed	Number of well-controlled asthma weeks.	Rates and time to first severe and moderate exacerbation, ACQ-5, FEV_1, AQLQ, medication use
SYGMA 2 (50)	4215	≥12 years	Phase 3, double blind, randomized parallel group	52 weeks	1. Placebo bid with Bud/form as needed 2. Bud bid with terbutaline as needed	Annual rate of severe exacerbations	Time to first severe exacerbation, steroid use, FEV_1, ACQ-5, AQLQ, medication use
Novel START (51)	675	18-75 years	Phase 3, open label, randomized parallel group	52 weeks	1. Salbutamol as needed 2. Bud bid with salbutamol as needed 3. Bud/Form as needed	Annual rate of exacerbations	Number of severe exacerbations, time to first exacerbation, ACQ-5, FeNO, medication use
PRACTICAL (54)	890	18-75 years	Phase 3, open label, randomized parallel group	52 weeks	1. Bud/Form as needed 2. Bud bid with terbutaline as needed	Number of severe exacerbations	Time to first severe exacerbation, FEV_1, FeNO, ACQ-5.

Study Name (Ref #)	Patient Number	Age	Design	Duration	Treatment groups	Primary Outcome	Secondary Outcomes
BEST (43)	455	18-65 years	Phase 3, double blind, randomized parallel group	26 weeks	1. Salbutamol as needed 2.BDP/salbutamol as needed 3. BDP bid with salbutamol as needed 4. BDP/salbutamol bid with salbutamol as needed	Peak expiratory flow rates (PEFR)	Exacerbation rate, daytime and nighttime symptoms, rescue medication use,
TREXA (44)	843	5-18 years	Phase 3, double-blind randomized parallel group	44 weeks	1. Salbutamol as needed 2. BDP/salbutamol as needed 3. BDP bid with BDP/salbutamol as needed 4. BDP bid with salbutamol as needed	Time to first severe exacerbation	Linear growth, FEV_1, FeNO, symptoms, asthma control, medication use
BASALT (45)	342	>18 years	Phase 3, double-blind randomized parallel group	38 weeks	1.physician assessment-based adjustment 2. biomarker-based adjustment 3. symptom-based adjustment, ICS taken with each albuterol rescue.	Time to treatment failure	Treatment failure rates, mean monthly ICS use, asthma exacerbations, lung function, symptoms, sputum eosinophils.

Study Name (Ref #)	Patient Number	Age	Design	Duration	Treatment groups	Primary Outcome	Secondary Outcomes
ASIST (46)	206	6–17 years	Phase 4, open-label randomized parallel group	12 months	1. Symptom-based adjustment, BDP taken with each albuterol rescue use 2. Guideline-based adjustment by primary care providers	Change in symptom control (ACT or cACT) at 12 months	Average monthly BDP dose; proportion with ≥1 exacerbation; change in quality of life; change in pre-bronchodilator FEV_1 % predicted; number of missed school days for asthma; change in ACT or cACT at 6 months
Lazarinis et al (56)	66	>12 years	Phase 2, double-blind randomized placebo-controlled, parallel group	6 weeks	1. Placebo once daily and BUD/FORM as-needed 2. Placebo once daily and terbutaline as needed 3. BUD once daily and terbutaline as needed	Change in maximal post-exercise decrease in FEV_1 after 6 weeks	Change in maximal post-exercise FEV1 fall after 3 wks, ACQ-5, symptoms, use of as-needed medications before exercise and for symptom relief

ACT: Asthma Control Test; c-ACT: childhood Asthma Control Test; GINA: Global Initiative for Asthma; BUD/FORM: budesonide/formoterol; BDP: beclomethasone dipropionate; bid: twice daily dosing; ACQ-5: asthma control questionnaire-5; AQLQ: asthma quality of life questionnaire; FEV_1: forced expired volume in 1 second; FeNO: fraction of exhaled nitric oxide.