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Research Article

Budesonide-Formoterol as Needed for The Treatment of Mild Persistent Asthma

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ABSTRACT

Objective: To summarize literature assessing the safety and efficacy of budesonide/formoterol, a low dose inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) used as needed for the treatment of adult patients with mild persistent asthma requiring step 2 therapy compared to low dose inhaled corticosteroid (ICS) plus short-acting beta agonist (SABA) and SABA monotherapy.

Data Sources: A literature search of PubMed (1966-October 2020), EMBASE (1973-October 2020) and clinicaltrials.gov was conducted using the following search terms: budesonide, formoterol, as needed, and mild asthma.

Study selection and data extraction: Randomized, controlled trials with data describing as needed use of budesonide-formoterol in the treatment of mild, persistent asthma were included.

Data synthesis: Current trials demonstrate a reduced risk of exacerbation and an improvement in symptom control in patients receiving budesonide/formoterol as needed when compared to as needed SABA alone. However, when compared to scheduled budesonide maintenance, patients receiving budesonide/formoterol as needed experienced worse symptom control and mixed exacerbation results.

Relevance to patient care and clinical practice: This review evaluates the efficacy and safety of budesonide/formoterol as needed for patients with mild asthma. The Global Initiative for Asthma (GINA), a global strategy for asthma management and prevention adopted this change in 2019, and the most recent updated Expert Panel Report 4 of the National Asthma Education and Prevention Program (NAEPP) did not address this area.

Conclusions: Based on this review of the literature, further study is needed to determine the place in therapy for budesonide/formoterol as needed in the treatment of mild persistent asthma. Low-dose ICS should remain the standard of therapy in patients with mild asthma requiring Step 2 therapy.

KEYWORDS

Asthma; Beta-2-adrenergic agonists; Corticosteroids, Inhaled; Pulmonary; Inhalers; Bronchodilators.

Introduction

Mild asthma is quite common, affecting 50-75% of patients with asthma [1]. Multiple guidelines exist to guide decision-making regarding treating patients with both intermittent and persistent asthma. Providers in the United States may follow guidelines that were created by the National Asthma Education and Prevention Program (NAEPP). The Expert Panel Report 4 (EPR-4) was recently published in December 2020, marking the first update since the Expert Panel 3 (EPR-3) was released in 2007 [2,3]. International asthma guidelines are developed by the Global Initiative for Asthma (GINA) and are updated annually; most recently in 2021 [4]. The NAEPP EPR-3 and 2018 version of the GINA guidelines had similar recommendations for management of mild asthma, which included the use of a short-acting beta-agonist (SABA), such as albuterol or terbutaline, as needed in patients requiring Step 1 therapy and use of daily low-dose inhaled corticosteroids (ICS) in patients requiring Step 2 therapy (Table 1) [2,3,5]. Use of a SABA as needed for symptom relief was also recommended in both guidelines. However, in 2019 (and carried forward to the 2020 and 2021 versions), worldwide GINA guidelines provided significant changes in their management recommendations, suggesting the use of low dose ICS-formoterol, a long-acting beta agonist (LABA), for symptom relief to be used as needed in Step 1 and 2 [4]. NAEPP EPR-4 does not recommend the use of low-dose ICS and formoterol as needed for rescue therapy for Step 1 or 2 [3]. Instead, the use of as-needed SABA and low-dose maintenance ICS is recommended for patients requiring Step 2 therapy. EPR4, however, does recommend single maintenance and reliever therapy (SMART) with ICS-formoterol for steps 3 and 4 whereas a SABA is still the recommended rescue therapy for steps 5 and 6. The rationale provided by GINA guidelines is that patients with mild asthma still experience inflammation, which necessitates the use of an inhaled corticosteroid [6]. GINA cited the most important considerations in making their recommendation was to prevent severe exacerbations and avoid the need for daily ICS in patients with mild asthma [4]. Adherence to asthma maintenance medications can be poor, which leads to untreated inflammation and an increased risk of exacerbation [7]. A 2015 systematic review found the mean level of adherence to ICS therapy to be 22 to 63%, and having mild asthma is a reason for poor adherence [7]. Increased use of SABA medications like albuterol has also been linked to an increased risk of exacerbation [8]. A retrospective review of prescription claims data found that patients obtaining 3 or more SABA refills in a 12 month period had a higher risk of experiencing an asthma exacerbation [8].

Formoterol is a LABA that is commercially available in the United States in two combination devices that also contain an inhaled corticosteroid; budesonide (Symbicort®) and mometasone (Dulera®). Formoterol's unique pharmacokinetic properties lend itself well for as needed use with a rapid onset within 5 minutes, which is similar to the onset of albuterol [9,10]. The duration of albuterol's effect is 4-6 hours; formoterol's duration is 12 hours providing an advantage of prolonged bronchodilation. This review will highlight the available literature on using LABA/ICS (specifically budesonide/formoterol) as needed for the treatment of mild persistent asthma in adults.

Literature search

A literature search was conducted by study investigators consisting of a PubMed (1966-October 2020), EMBASE (1973-April 2021), and clinicaltrials.gov database search of articles using the search terms budesonide, formoterol, as needed, and mild asthma. Randomized controlled trials published in English with data describing as needed use of budesonide-formoterol in the treatment of mild, persistent asthma were reviewed from database inception to April 2021. Articles that only included daily maintenance therapy with budesonide/formoterol were excluded. The bibliographies of these articles were then reviewed for inclusion of other relevant articles not included in the prior database search. There is currently no other published literature assessing the efficacy and safety of other ICS/LABA combination inhalers, thus other inhaler combinations were not included in this search. Two investigators (EBW, EFC) independently reviewed all identified titles and abstracts, and the third investigator (AY) ensured that studies met study inclusion criteria. Any discrepancies in question for inclusion were reviewed by investigators and resolved by consensus. Fourteen randomized controlled trials were obtained in the literature search, and four

Table 1: Asthma management [2-5].

Severity classification	Step	Preferred treatment			
		NAEPP EPR3 [3]	GINA 2018 [5]	GINA 2020 [4]	NAEPP EPR4 [2]
NAEPP: intermittent[a] GINA: mild persistent[b]	1	SABA PRN	SABA PRN; consider low-dose ICS	Low-dose ICS + formoterol PRN	SABA PRN
NAEPP: Mild persistent[c]	2	Low-dose ICS	Low-dose ICS	Low-dose ICS or low-dose ICS + formoterol PRN	Low-dose ICS or concomitant ICS and SABA PRN
Relief medication		SABA PRN	Step 1-2: SABA PRN	Low-dose ICS + formoterol PRN	SABA PRN

NAEPP: National Asthma Education and Prevention Program; GINA: Global Initiative for Asthma; SABA: short acting beta agonist; PRN: as needed; ICS: inhaled corticosteroid

[a]Defined as daytime symptoms two days per week or less, nighttime awakenings two or fewer times per month, use of short acting beta-agonist (SABA) no more than twice per week, and no interference with normal activity

[b]GINA guidelines assess asthma severity retrospectively from level of treatment required to control symptoms and exacerbations and includes assessment of daytime symptoms, nighttime awakenings, use of reliever therapy, and activity limitation in the past four weeks.

[c]*Defined as daytime symptoms more than two days per week but not daily, nighttime awakenings three to four times per month, use of short acting beta-agonist (SABA) more than twice per week but not daily and not more than once on any day, and minor interference with normal activity.

Table 2: Summary of study designs [11,12,16,17].

	SYGMA-1 [11]	SYGMA-2 [12]	Novel-START [16]	PRACTICAL [17]
Trial design	Double blind, randomized, parallel-group, phase 3 trial	Double blind, randomized, parallel-group	Randomized, open-label, parallel-group, controlled trial	Randomized, open label, parallel group, controlled trial
Trial duration	52 weeks	52 weeks	52 weeks	52 weeks
Trial site	18 countries, did not include the United States	25 countries, did not include the United States	New Zealand, United Kingdom, Italy, Australia	New Zealand
Patient population	-Age ≥12 years old -Diagnosis of asthma according to GINA criteria -In need of GINA step 2 therapy	-Age ≥12 years old -Diagnosis of asthma according to GINA criteria -In need of GINA step 2 therapy	-18-75 years old -Diagnosis of asthma from physician -Use of SABA as sole asthma therapy in previous 3 months -Patient reported use of SABA on at least two occasions in the previous 4 weeks	-18-75 years old -Diagnosis of asthma from physician -If on SABA, need for use on at least 2 occasions in past 4 weeks or waking because of asthma at least once in previous 4 weeks or history of severe exacerbation requiring oral corticosteroids in previous 52 weeks -If on ICS, partly or well controlled asthma per 2014 GINA guidelines
Exclusion criteria	-Use of oral glucocorticoids within 30 days prior to enrollment -Use of beta blockers -History of life-threatening asthma including intubation and ICU admission -Pregnancy	-Change in asthma treatment or systemic glucocorticoids within 30 days prior to enrollment -Current or former smoker (≥ pack years) -History of life-threatening asthma	-Self-reported use of medications other than SABA in previous 3 months -Hospitalization for asthma in previous 12 months -Patient reported smoking history of more than 20 pack-years or the onset of respiratory symptoms after age 40 -Pregnancy	-Oral corticosteroid use in previous 6 weeks or home supply of oral corticosteroids -Self-reported use of other medications for asthma -ICU admission for asthma -≥20 pack year history or onset of respiratory symptoms after age 40 -Pregnancy
Total number of patients who underwent randomization	3363	4176	666	885
Treatment arms	Placebo BID + B/F PRN 200/6 mcg 1 puff Placebo BID + T PRN 0.5 mg 1 puff Bud 200 mcg BID + T PRN 0.5 mcg	Placebo BID + B/F PRN 200/6 mcg ; Bud 200 mcg BID + T PRN 0.5 mg	B/F PRN 200/6 mcg PRN Alb PRN 100 mcg 2 puffs Bud 200 mcg BID + Alb PRN 100 mcg 2 puffs	B/F PRN 200/6 mcg 1 puff Bud 200 mcg BID + T PRN 250 mcg 2 puffs
Primary outcome	Superiority of budesonide/formoterol vs terbutaline for mean percentage of electronically recorded weeks with well-controlled asthma	Non-inferiority of budesonide/formoterol PRN vs budesonide maintenance for annualized rate of severe exacerbations	Annualized rate of asthma exacerbations per patient	Number of severe exacerbations per patient per year

GINA: Global Initiative for Asthma; ICU: intensive care unit; BID: twice daily; PRN: as needed; SABA: Short Acting Beta Agonist; ICS: Inhaled Corticosteroid; B/F PRN: Budesonide/Formoterol as needed; Alb PRN: Albuterol as needed; B/F M: Budesonide/Formoterol daily Maintenance; T PRN: Terbutaline as needed; Bud: Budesonide Maintenance.

were included in this review, with ten articles being excluded due to only including daily maintenance therapy with budesonide/formoterol.

SYGMA 1, SYGMA 2 [11,12]

The Symbicort Given as Needed in Mild Asthma (SYGMA-1 and SYGMA-2) trials evaluated the efficacy and safety of budesonide/formoterol use as needed in patients with mild asthma [11,12]. In SYGMA-1, patients were randomized to receive: twice daily placebo maintenance + budesonide/formoterol dry powder inhaler (DPI) as needed for symptom control (n = 1277), twice daily placebo maintenance + terbutaline DPI as needed (n = 1277), or twice daily maintenance low-dose budesonide DPI and terbutaline DPI as needed (n = 1282) (Table 2). The primary outcome was mean percentage of weeks with electronically recorded well-controlled asthma by patient report, which was based on as needed inhaler use, recorded asthma symptoms, nighttime awakenings, peak expiratory flow, and additional use of inhaled or systemic glucocorticoids. Asthma was considered well-controlled if patients had no nighttime awakenings due to asthma and no additional inhaled and/or systemic glucocorticoid treatment due to asthma as well as two or more of the following: no more than two days with an asthma symptom score of >1, no more than two days of as-needed medication use, or morning peak expiratory flow >80% predicted each day. Patients used an electronic diary to record data and the system prompted the use of their blinded maintenance inhaler. The budesonide/formoterol as needed group experienced a significantly higher mean percentage of weeks with well controlled asthma across the 52 week study timeframe compared to terbutaline as needed throughout the study period (34.4% vs 31.1%, OR 1.14, CI 1.00-1.30, p = 0.046). However, there was no difference between budesonide/formoterol as needed and budesonide maintenance in relation to weeks with well controlled asthma (34.4% vs 44.4%, OR 0.64, CI 0.57-

Table 3: Summary of outcomes related to as-needed budesonide/formoterol PRN arm [11,12,16,17].

	SYGMA-1 [11]	SYGMA-2 [12]	Novel-START [16]	PRACTICAL [17]
	Baseline characteristics (for as-needed B/F arm)			
Age (years)	39.8	41.3	36	43.3
Female sex – (%)	60.8	62.6	55.5	56
ACQ-5 score – mean	1.57	1.49	1.1	1.1
Therapy prior to enrollment (%) **SABA** **Low dose ICS**	 44.2 55.8	 45.9 54.1	 100 0	 30 70
Patient reported SABA use in 4 weeks before enrollment (occasions/week) - mean	--	--	3.8	4.3
SABA use <2x/week prior to enrollment (%)	--	--	48	--
Severe exacerbation in previous 12 months – (%)	20.1	22	5.5	12
	Results			
Primary outcome	Weeks of well controlled asthma: B/F PRN vs T PRN: 34.4% vs 31.1%, p = 0.046	Annualized rate of severe asthma exacerbations: B/F PRN vs Bud: 0.11 vs 0.12 (p= 0.75 for superiority)	Annualized rate of asthma exacerbations per patient B/F PRN vs Alb PRN: 0.195 vs 0.400, p <0.001 B/F PRN vs Bud: 0.195 vs 0.175, p = 0.65	Severe exacerbations per patient per year: B/F PRN vs Bud: 0.119 vs 0.172, p = 0.049
	Secondary outcomes			
Severe exacerbations	B/F PRN vs T PRN: 5.6 vs 11.9%, p < 0.001 B/F PRN vs Bud: 5.6 vs 6.1%, p = 0.28	B/F PRN vs Bud: 8.5 vs 8.8%, p=0.66	B/F PRN vs Alb PRN: 21 vs 23 B/F PRN vs Bud: 21 vs 9 P values not reported	--
Moderate to severe exacerbations	B/F PRN vs T PRN: 10.3 vs 21.5%, p<0.001 B/F PRN vs Bud: 10.3 vs 11.2, p = 0.66	--	--	Expressed as per patient per year 0.165 vs 0.237, p = 0.024
Adherence to twice daily therapy	79%	64%	56%	76%
Mean daily ICS dose (mcg)	B/F PRN 57 vs Bud 340	B/F PRN 103.5 vs Bud 250.6	B/F PRN 107 vs Bud 222	176 vs 302
# beta-agonist actuations per day	--	B/F PRN vs Bud: 0.52 vs 0.49	B/F PRN vs Alb PRN vs Bud : 0.5 vs 1 vs 0.5	B/F PRN vs Bud: 0.9 vs 0.5

SABA: Short-acting beta-agonist; ICS: Inhaled Corticosteroid; ACQ-5: Asthma Control Questionnaire; B/F PRN: Budesonide/formoterol as needed; Alb PRN: Albuterol as needed; T PRN: Terbutaline as needed; Bud: Budesonide Maintenance.

0.73, p value not reported) (Table 3). A post-hoc analysis found patients that used two or more puffs of budesonide/formoterol as needed in one day had a reduced risk of severe exacerbation in the following 21 days [13]. ACQ-5 was significantly reduced in patients receiving budesonide/formoterol as needed compared to terbutaline alone, however budesonide maintenance had a larger reduction in symptom score compared to budesonide/formoterol as needed. Adverse events occurred more frequently in patients receiving terbutaline as needed (42.7%) vs budesonide/formoterol as needed (38%) and budesonide maintenance (39.9%), with the most common symptoms including asthma (109 [8.5%] vs 37 [2.9%] vs 57 [4.4%], respectively) and upper respiratory tract infections (76 [6%] vs 71 [5.6%] vs 93 [7.3%], respectively). The study authors concluded that budesonide/formoterol as needed is more effective than SABA monotherapy in patients with mild asthma for symptom control and prevention of moderate-to-severe and severe exacerbations. However, the use of budesonide/formoterol as needed when compared to budesonide maintenance is inferior in achieving well controlled asthma with no difference in exacerbation prevention. This study had several limitations that decrease the generalizability of the results. Terbutaline was used as the SABA agent in this trial, which is not available in the United States. One component of the primary outcome, weeks of well controlled asthma, indicated patients could not experience any episodes of nighttime awakenings due to asthma. Per NAEPP guidelines, patients are considered to have well controlled asthma if they experience less than two nighttime awakenings per month, which is less strict than study criteria [3,4]. The daily asthma symptom score was created for this study and is not a validated tool like the Asthma Control Questionnaire (ACQ) [14,15]. Patients included in this trial were indicated for Step 2 therapy because they had failed intermittent SABA therapy or were controlled on maintenance ICS therapy. Thus, the patients randomized to the SABA only group were uncontrolled and undertreated throughout the study, possibly contributing to more exacerbations and fewer weeks with well controlled asthma. Adherence rates to maintenance corticosteroid therapy was higher than what has been reported in clinical practice, which could have contributed to more weeks with well controlled asthma.

Similar to SYGMA-1, SYGMA-2 was an international trial of similar design [12]. Patients were randomized to receive twice daily placebo + budesonide/formoterol DPI as needed (n = 2087) or twice daily maintenance low-dose budesonide DPI and terbutaline DPI as needed (n = 2089) (Table 2). Unlike SYGMA-1, patients did not record daily asthma symptoms or receive daily prompts to encourage use of maintenance therapy. For the primary outcome, the budesonide/formoterol as needed group was non-inferior to budesonide maintenance therapy for the annualized rate of severe exacerbations (0.11 vs 0.12, OR 0.97, one-sided 95% upper confidence limit 1.16, and p value not reported), but did not meet the criteria for superiority (OR 0.97, 95% CI 0.78-1.20, p = 0.75). A severe exacerbation was defined as worsening asthma leading to systemic glucocorticoid treatment for ≥3 days, hospitalization, or an emergency department visit with use of systemic glucocorticoids. There were no significant differences between groups in time to first severe asthma exacerbation (HR 0.96, 95% CI, 0.78-1.17). The study authors concluded that budesonide/formoterol as needed is non-inferior to low-dose budesonide maintenance in annualized rate of severe exacerbation. However, budesonide maintenance therapy showed statistically significant improvement in secondary outcomes like the asthma control questionnaire-5 (ACQ-5), asthma quality of life questionnaire (AQLQ), and forced expiratory volume in 1 second (FEV-1) before bronchodilator use. Requiring the use of scheduled placebo in both SYGMA-1 and SYGMA-2 trials, all treatment groups were required to use a maintenance inhaler twice daily, even if the patient was randomized to an as needed group, which would not apply in clinical practice.

Novel-START [16]

The Novel Symbicort Turbuhaler Asthma Reliever Therapy (Novel-START) trial evaluated the efficacy of budesonide/formoterol use as needed in patients previously prescribed SABA monotherapy for the treatment of mild asthma in New Zealand, the United Kingdom, Italy, and Australia. Patients were randomized to receive one of three treatments: budesonide/formoterol DPI as needed for symptom control (n = 225), albuterol metered dose inhaler (MDI) as needed for symptom control (n = 223), or twice daily maintenance low-dose budesonide DPI + albuterol MDI as needed (n = 220) (Table 2). For the primary outcome, patients receiving budesonide-formoterol as needed experienced a significantly reduced annual exacerbation rate per patient compared to albuterol as needed (0.195 vs 0.400, RR 0.49, CI 0.33-0.72, p <0.001). There was no difference in annual exacerbation rate when comparing budesonide/formoterol as needed to budesonide maintenance (0.195 vs 0.175, RR 1.12, CI 0.70-1.79, p = 0.65) (Table 3). An exacerbation in this trial was defined as an urgent consultation, prescription for systemic glucocorticoids, or high beta agonist use (> 16 puffs albuterol/day or > 8 puffs budesonide/formoterol/day). Adverse events occurred similarly across all groups, with 185/226 81.9% of patients experiencing adverse events in the terbutaline group, 83.7% in the budesonide maintenance group, and 78.4% in the budesonide-formoterol as needed group. The most common adverse events included upper respiratory infections (75 [33.2%] vs 75 [33%] vs 71 [33.2%], respectively), nasopharyngitis (46 [20.4%] vs 35 [15.4%] vs 47 [21.2%], respectively), and asthma (46 [20.4%] vs 26 [11.5%] vs 17 [7.5%] respectively). The study authors concluded that budesonide/formoterol as needed reduced the rate of annual exacerbation and resulted in fewer severe exacerbations compared to SABA therapy in patients with mild asthma previously receiving SABA monotherapy. There was no difference between budesonide/formoterol as needed and budesonide maintenance in rate of annual exacerbations; however, patients receiving budesonide/formoterol maintenance therapy had fewer severe exacerbations (Table 3). There were some limitations to this trial including the variation in the definition of an exacerbation compared to national and international guidelines. While the use of albuterol is more generalizable than the use of terbutaline in SYGMA-1, patients in the albuterol as needed group averaged one puff of albuterol daily. With this average albuterol use, we assume this would be not well controlled per NAEPP EPR3 and EPR4 guidelines since patients appeared to require more than 2 days per week and possibly require a step up in therapy per NAEPP EPR3 and EPR4 guidelines [2,3]. Patients receiving budesonide maintenance group had an adherence rate of 57%, which, while more closely mirroring real world adherence, could have resulted in undertreatment.

PRACTICAL [17]

The Personalized Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist (PRACTICAL) trial evaluated the efficacy of as needed budesonide/formoterol DPI reliever therapy compared to maintenance budesonide DPI therapy plus as needed terbutaline DPI in patients with mild to moderate asthma. Patients were randomized to receive either budesonide/formoterol as needed for symptom control (n = 437) or twice daily maintenance low-dose budesonide and terbutaline as needed for symptom control (n = 448). For the primary outcome, patients receiving budesonide-formoterol as needed experienced a significantly lower number of severe asthma exacerbations per patient per year compared to patients receiving budesonide maintenance (0.119 vs 0.172, RR 0.46, CI 0.48-1.00, p=0.049). A severe exacerbation was defined as use of systemic corticosteroids for at least three days because of asthma, or admission to hospital or an emergency department visit because of asthma requiring systemic corticosteroids. Adverse events occurred more frequently in the budesonide/formoterol PRN group (87.5 vs 82.8%, p=0.05), with the most common adverse events including nasopharyngitis, asthma, upper and lower respiratory tract infections. The study authors concluded that as needed budesonide/formoterol reliever therapy reduced the annual rate of severe and moderate to severe exacerbations compared to patients receiving maintenance budesonide therapy. A subset of patients enrolled in the trial (n=110) received inhalers with electronic monitoring of inhaler usage and in this group, there was a 31% decrease in exacerbations in the as needed groups. This group also used 40% less budesonide compared to the maintenance group. However, the mean dose of 176 mcg/d used by the as needed group is near the low end of the low dose ICS range of budesonide of 180-540 mcg/d. Limitations included open label

design and use of terbutaline as the SABA in both groups. Patients receiving budesonide/formoterol as needed used on average 0.9 actuations of their rescue inhaler per day, which would necessitate changes in therapy as per NAEPP ERP4, so these patients were possibly undertreated [2].

Relevance to Patient Care and Clinical Practice

Review of the use of budesonide/formoterol as needed for the treatment of mild asthma demonstrated a reduced risk of exacerbation and an improvement in symptom control when compared to as needed SABA alone. However, the patients studied were possibly undertreated. When compared to scheduled budesonide maintenance, patients receiving budesonide/formoterol as needed experienced worse symptom control but do not appear to increase the risk of severe exacerbations. Overall, the findings of these trials are clinically significant as exacerbation lowering can be meaningful in the quality of life and financial burden of patients, caregivers, and hospital systems. There are other considerations for clinical practice that should be noted.

All studies discussed in this review took place in countries outside of the United States where the Turbuhaler® device (a DPI) is common and was used in all four clinical trials. The Turbuhaler® is not available in the United States; budesonide/formoterol is available only in a metered-dose inhaler (MDI). It is unknown if results will fully translate when using the MDI version of the drug, as similarities and differences exist between the two devices. The onset of the DPI and MDI are 3 and 5-10 minutes, respectively, so the onset would be slightly longer but still quick in patients receiving the MDI product. Also, budesonide/formoterol does not have an FDA approved indication for as needed use in the United States. This could pose a challenge for patients when seeking coverage by their insurance plan. Other cost considerations include the expiration date of the product. Budesonide/formoterol MDI expires 3 months after removal from the foil pouch; therefore, at minimum, patients must purchase 4 inhalers per year to use as needed [9]. However, many DPI's have a longer expiration date after initial use, which could provide cost savings. This can potentially increase both payer and out of pocket (copay) cost significantly compared to using an albuterol inhaler. The cost of one budesonide/formoterol device is much more than an albuterol inhaler ($437.26 vs $74.02, which could limit real world generalizability and affordability [18,19]. The price of budesonide/formoterol, however, is similar to that of budesonide alone ($300-500), and budesonide/formoterol as needed was found to be a cost-effective alternative compared to low-dose ICS [20,21]. The cost of an emergency department visit related to asthma is approximately $1400, and the higher cost of asthma medications has been correlated with better asthma control and significantly lower total asthma costs [21-23]. The mean daily dose of ICS was lower in patients receiving budesonide/formoterol as needed compared to budesonide maintenance. While inhaled glucocorticoids have fewer adverse effects than systemic glucocorticoids, concerns can arise with use over many years and when higher doses are administered to patients of extremes of age, including thrush, dysphonia, adrenal suppression, reduction in bone mineral density, and glaucoma [9]. Patients preferred using as needed reliever therapy over scheduled treatment. However, patients also noted reduction in shortness of breath and lower risk of asthma flare as being important factors in relation to their asthma management [24,25].

More studies are needed to determine the place in therapy for other potential as-needed LABA/ICS combination products, including mometasone/formoterol and fluticasone/vilanterol, which also have a rapid onset of effect and prolonged duration of action. Pediatric and pregnant patients were excluded from the reviewed trials, so it is unclear what role as needed ICS/LABA plays for these patients moving forward.

While GINA guidelines have fully embraced and recommend the use of low-dose ICS/formoterol as needed, it is still unclear at this time if and when the United States guidelines will follow suit [2,3]. NAEPP EPR-4 did not adopt this shift in recommendation or cite any of the literature reviewed in this article [2]. European guidelines, however, have endorsed the use of single maintenance and reliever therapy (SMART therapy), which consists of the use of an inhaled corticosteroid and LABA scheduled and as needed for moderate and severe asthma for years [26,27].

Conclusion

As needed budesonide/formoterol for the treatment of mild asthma demonstrated a reduced risk of exacerbation and an improvement in symptom control when compared to as needed SABA alone. However, studies that were included in this review demonstrated that scheduled maintenance therapy provides a significant improvement in asthma control, quality of life measures, and lung function. Also, patients enrolled and randomized to the PRN ICS/LABA groups may have been undertreated. Without an FDA approved indication for as needed use and until further studies can be conducted with the MDI inhaler, budesonide/formoterol should continue to be used scheduled twice daily as maintenance controller therapy. Scheduled low-dose ICS should remain the standard of care in patients with mild asthma requiring Step 2 therapy.

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