THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
April 2022 Volume 12 Issue 3

Asthma Guidance Update with a Focus on Changes for Managing Patients with Mild Asthma

Kathy Sentena, Pharm.D., Oregon State University Drug Use Research and Management Group

Asthma is a common illness affecting over 11% of Oregonians with a higher prevalence among those on the Oregon Health Plan (OHP).[1,2] The incidence of asthma emergency department visits is approximately 50 per 10,000 individuals per year in the United States (U.S.), representing substantial morbidity and cost to the health care system.[3] In 2013 the total cost of asthma in the U.S. was $81.9 billion.[4] Annual prescription medications for asthma accounted for the highest per-person expense, estimated at $1,830 based on 2015 dollars.[4]

Controlling asthma symptoms through reductions in exacerbations is a primary target of asthma management. Recommendations for managing asthma have recently been revised by the Global Initiative for Asthma (GINA).[5] Inhaled corticosteroids (ICS)/rapid onset long-acting beta-agonists (LABA) are referred to as single maintenance and reliever therapy (SMART) or maintenance reliever therapy (MART). This combination is being used to manage patients with persistent asthma and more recently also recommended as reliever therapy for patients with mild asthma.[5,6] Budesonide/formoterol is used for this purpose due to the pharmacokinetics of formoterol, which provides a quick onset suitable for reliever therapy and budesonide as the anti-inflammatory component. The purpose of this newsletter is to review the evidence and recommendations for mild asthma.

Evidence for ICS/formoterol as Reliever Therapy

Evidence has demonstrated that combination ICS and rapid acting LABA (e.g., budesonide/formoterol), used as reliever therapy reduces asthma exacerbations requiring medical visits or systemic corticosteroids, compared to short-acting beta-agonist (SABA) reliever therapy.[5] Additional data suggests that this combination improves asthma control and quality of life, with less reliance on adherence to daily maintenance therapy. A steroid-sparing effect with budesonide/formoterol may prevent adverse events related to systemic corticosteroid exposure. Studies have found no increase in adverse events with budesonide/formoterol therapy compared to daily ICS or ICS/LABA used with SABA for symptom relief.[5] Specifics on evidence used to support the use of budesonide/formoterol as reliever therapy are displayed in **Table 1**.

Table 1. Evidence for the Use of Budesonide/formoterol as Reliever Therapy

Study Design	Results	Strength of Evidence
Beasely, et al[7] (n=668), START		
DB, PC, OL, PG, RCT Adult patients with mild asthma 52 weeks	**Annualized exacerbation* rate:** • Albuterol 100mcg as needed: 0.400 • Budesonide 200mcg twice daily + as needed albuterol: 0.175 • Budesonide 200mcg/ formoterol 6 mcg as needed: 0.195 Budesonide/formoterol vs. albuterol: RR 0.49; 95% CI, 0.33 to 0.72; P<0.001 Budesonide/formoterol vs. budesonide: RR 1.12; 95% CI, 0.70 to 1.79; P = 0.65	Low
O'Byrne,et al[8] (n=3836), SYGMA 1		
DB, PG RCT Patients 12 and older with mild asthma 52 weeks	**Mean percentage of weeks with well controlled asthma per patient†:** • Placebo twice daily + terbutaline 0.5mg as needed: 31.1% • Placebo twice daily + budesonide 200mcg/ formoterol 6 mcg as needed: 34.4% • Budesonide 200mcg twice daily + terbutaline 0.5mg as needed: 44.4% Budesonide-formoterol vs. terbutaline: OR 1.14; 95% CI, 1.00 to 1.30; P=0.046	Moderate
Bateman, et al[9] (n=4176), SYGMA 2		
DB, PG, Phase 3, RCT Patients 12 and older with mild asthma 52 weeks	**Annualized rate of severe exacerbations:** • Placebo twice daily + budesonide 200mcg/ formoterol 6mcg as needed: 0.11 • Budesonide 200mcg twice daily + terbutaline 0.5mg as needed: 0.12 Noninferiority margin was set at 1.2 Rate ratio: 0.97; upper one-sided 95% confidence limit 1.16	Low
Key: * Exacerbation that required one or more of the following: an urgent medical care consultation, a prescription of systemic glucocorticoids, or an episode of high beta-agonist use; † As needed therapy was used to determine symptom control as measured via an electronic patient diary with asthma symptom scores, night-time awakenings, morning peak expiratory flow, inhaler-monitor data, and		

an electronic case-report form for the additional use of inhaled or systemic glucocorticoids.
Abbreviations: CI = confidence interval; DB = double blind; OL = open-label; PC = placebo controlled; PG = parallel group; RCT = randomized controlled trial; RR = relative rate.

Budesonide/formoterol reduced exacerbation rates as demonstrated by the primary endpoint in the START and SYGMA 2 studies and as a secondary endpoint in the SYGMA 1 study, which found a reduction with the use of low dose budesonide/formoterol compared to as-needed SABA (relative rate [RR] 0.40; 95% confidence interval [CI], 0.18 to 0.86; p<0.05).[7] Scheduled maintenance budesonide therapy was more effective in reducing asthma exacerbations compared to as-needed budesonide-formoterol.[7,8]

The START trial results are limited by a high chance of performance bias, due to the open label design. SYGMA 2 was a noninferiority trial that started out as a superiority trial; however, a change in trial design was made due to exacerbation rates which were lower than expected and high adherence to maintenance therapy. The primary endpoint was calculated based on the full analysis set; however, use of the per protocol population is a more accurate assessment of efficacy in a noninferiority trial. Both SYGMA trials and the START trial were funded by AstraZeneca, the manufacturer of Symbicort (budesonide/formoterol) and Pulmicort (budesonide).

Budesonide/formoterol Policies and Best Practices

- Adolescent and adult dose of budesonide/formoterol:
  - **Reliever therapy**: 160/4.5 mcg as needed
  - **MART**: up to 54 mcg metered dose of formoterol
- Budesonide/formoterol should not be used with other LABAs or ICS/LABA combination products
- Budesonide/formoterol is a preferred therapy for Fee-for-Service (FFS) Oregon Health Plan (OHP) patients

Guideline Recommendations

Treatment recommendations for individuals with asthma are based on symptoms and divided into steps. Asthma guidelines recommend therapies based on intermittent or persistent symptoms; however, preferred therapy for each step may differ according to the guideline in which recommendations are based (**Table 2**).

Table 2. Asthma Treatment Guideline Recommendations for Adolescents and Adults*[5,10,11]

Steps	Guideline	Treatment Recommendations
Step 1	GINA	As-needed low dose ICS-formoterol or As-needed SABA with ICS
	NAEPP	SABA as-needed
	NICE+	SABA as-needed
Step 2	GINA	As-needed low dose ICS-formoterol or low-dose maintenance ICS
	NAEPP	Low-dose ICS and SABA as-needed OR Concomitant ICS and SABA as-needed
Step 3	GINA	Low dose maintenance ICS-formoterol or ICS/LABA with SABA as-needed
	NAEPP	Daily and as-needed combination low-dose ICS-formoterol
	NICE+	Daily ICS with SABA as-needed
Step 4	GINA	Medium dose maintenance ICS-formoterol or ICS/LABA with SABA as-needed
	NAEPP	Daily and as-needed combination medium-dose ICS-formoterol
	NICE+	MART regimen with low-dose ICS
Step 5	GINA	Add-on LAMA Consider high dose ICS-formoterol
	NAEPP	Daily medium- to high-dose ICS/LABA + LAMA and SABA as needed
	NICE+	Increase ICS dose to moderate maintenance dose
Step 6	NAEPP	Daily high-dose ICS/LABA + oral systemic corticosteroids + SABA as needed

Key: * Alternative treatment options are available in full guidelines; + Correlation of NICE recommendations to steps defined by other guidelines.
Abbreviations: GINA - Global Initiative for Asthma; ICS – inhaled corticosteroid; LABA – long-acting beta-agonist; MART - maintenance reliever therapy; NAEPP - National Asthma Education and Prevention Program; NICE - National Institute for Health and Care Excellence; SABA – short-acting beta-agonist.

Recent GINA recommendations separate reliever therapy recommendations for adults and adolescents with asthma into two tracks (**Table 3**).[5] The change was prompted by evidence that the risk of severe asthma exacerbations exists in individuals with intermittent symptoms and this population experiences risk reduction with ICS-containing treatment. For individuals requiring daily controller therapy, MART is recommended.[5] For children 6-11 years, an ICS is recommended whenever a SABA is used, if not taking a daily maintenance ICS.[5]

Table 3. Asthma Reliever Therapy Recommendations for Adults and Adolescents[5]

Track	Therapy	Rationale
Track 1	Low-dose ICS-formoterol as reliever therapy	Risk reduction in severe exacerbations with ICS-formoterol compared to SABA reliever alone*
Track 2	SABA as reliever therapy with instructions to take ICS when SABA is used†	Alternate approach if patient has no exacerbations on current therapy and is likely to be adherent to controller therapy

Key: * Preferred therapy; † If not taking daily maintenance ICS
Abbreviations: ICS = inhaled corticosteroid; SABA = short-acting beta-agonist

The National Institute for Health and Care Excellence (NICE) provides guidance on asthma treatment based on symptoms but does not base recommendations on steps, as designated by other guidelines. Short-acting beta-agonist monotherapy is recommended NICE for reliever therapy and for those with infrequent, short-lived wheeze and normal lung function in adult patients.[10] NICE recommends daily ICS treatment as first-line maintenance therapy for adult patients with asthma.[10] MART is recommended for adult patients who have uncontrolled asthma on low-dose ICS and LABA, with or without a leukotriene receptor antagonist (LTRA), as maintenance therapy.

In 2020 the National Asthma Education and Prevention Program (NAEPP) updated treatment recommendations for adolescents and adults based on a review done by the Agency for Healthcare Research and Quality (AHRQ).[11] No changes to the recommendations were made for individuals with intermittent asthma (Step 1) for the use of as-needed SABA. Daily low-dose ICS with a SABA or as-needed concomitant ICS and SABA is recommended for mild persistent asthma (Step 2). MART therapy is recommended as the preferred therapy for moderate persistent asthma (Step 3 and Step 4) as daily and for as-needed treatment.[11] This was a strong recommendation based on moderate certainty of evidence.[11]

Considerations for implementing MART therapy based on NAEPP recommendations[11]:

- Individual is taking Step 3 (low-dose ICS) or Step 4 (medium-dose ICS) treatment
- The dose of MART maintenance therapy is ICS/formoterol 1-2 puffs once or twice daily and 1-2 puffs as needed for asthma symptoms
- The recommended formoterol dose is 4.5 mcg/inhalation, based on trial data

Conclusion

There is evidence for improved symptom control with the use of budesonide/formoterol as reliever therapy and as MART in adolescent and adult patients with asthma. Guideline recommendations vary on the level of asthma symptoms necessitating the use of MART therapy. Benefits of MART include a reduced risk of severe exacerbations, reduced steroid exposure and less reliance on compliance to daily maintenance treatments.

Peer reviewed by: Shyam Joshi, M.D., Assistant Professor of Medicine, Section of Allergy and Clinical Immunology, School of Medicine, Oregon Health and Science University and Edward Saito, Pharm.D., BCACP, Associate Professor, Pacific University School of Pharmacy

References

1. Centers for Disease Control and Prevention. Most Recent Asthma State or Territory Data. 2019. Available at: cdc.gov/astha/most_recent_data_states.htm. Accessed February 9, 2022.
2. Oregon Health Authority. Asthma Among Oregon Health Plan Members. October 2017. Available at: www.oregon.gov/oha. Accessed February 11, 2022.
3. Centers for Disease Control and Prevention. Asthma Emergency Department (ED) Visits 2010-2018. Available at: cdc/gov/asthma/asthma_stats/asthma-ed-visits_2010-2018.html. Accessed February 11, 2022.
4. Nurmagambetov T, Kuwahara R, Garbe P. The Economic Burden of Asthma in the United States, 2008-2013. *Ann Am Thorac Soc*. 2018;15(3):348-356. doi:10.1513/AnnalsATS.201703-259OC
5. Global Initiative for Asthma. Global Strategy for Asthma Managment and Prevention, 2021. Available at: www.ginasthma.org. Accessed February 11, 2022.
6. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of Inhaled Corticosteroids and Long-Acting β-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. *JAMA*. 2018;319(14):1485-1496. doi:10.1001/jama.2018.2769.
7. Beasley R, Holliday M, Reddel HK, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. *N Engl J Med*. 2019;380(21):2020-2030. doi:10.1056/NEJMoa1901963
8. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *N Engl J Med*. 2018;378(20):1865-1876. doi:10.1056/NEJMoa1715274.
9. 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(20):1877-1887. doi:10.1056/NEJMoa1715275.
10. National Institute for Health and Care Excellence. Athma: diagnosis, monitoring and chronic asthma managment. NICE Guideline. November 2017. Available at: nice.org.uk/guidance/ng80. Acessed November 15, 2018.
11. Cloutier MM, Dixon AE, Krishnan JA, Lemanske RF, Pace W, Schatz M. Managing Asthma in Adolescents and Adults: 2020 Asthma Guideline Update From the National Asthma Education and Prevention Program. *JAMA*. 2020;324(22):2301-2317. doi:10.1001/jama.2020.21974.