FPIN's Clinical Inquiries

Effectiveness of ICS/LABA Compared With SABA as Relief Medications for Asthma

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Clinical Question

Is an inhaled corticosteroid (ICS)/long-acting $beta_2$ agonist (LABA) combination effective as a relief medication in patients with mild to severe asthma when compared with a short-acting $beta_2$ agonist (SABA)?

Evidence-Based Answer

In mild asthma, as-needed ICS/LABA combinations should be used instead of as-needed SABAs without a maintenance inhaler because ICS/LABAs decrease the risk of severe exacerbations, increase the likelihood of having well-controlled asthma, and prolong the time to a first severe exacerbation. (Strength of Recommendation [SOR]: A, consistent, good-quality randomized controlled trials [RCTs].) In moderate to severe asthma, ICS/LABA single maintenance and reliever therapy (SMART) can decrease the risk of severe asthma exacerbations. (SOR: A, systematic review and meta-analysis of homogenous RCTs.) SMART had similar outcomes to other treatment regimens (ICS/LABA plus SABA) for forced expiratory volume in one second (FEV_1), symptom control, and safety.

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Evidence Summary

A 2019 RCT lasting 52 weeks involved 668 patients 18 to 75 years of age with mild asthma who were from New Zealand and Europe. The trial compared the annualized rate of asthma exacerbations per patient in three treatment groups: ICS/LABA (budesonide/formoterol [Symbicort], one inhalation as needed); albuterol alone (100-mcg dose, two inhalations as needed from a pressurized metered dose inhaler); and budesonide (200 mcg, one inhalation twice daily) plus as-needed albuterol.[1] Two of the three arms focused on the reliever medication (n = 443). An exacerbation was defined as worsening asthma that resulted in one or more of the following: an urgent medical care consultation, prescription of systemic glucocorticoids for any duration, or an episode of high $beta_2$ agonist use (i.e., more than 16 actuations of albuterol or more than eight actuations of budesonide/formoterol over 24 hours). At 52 weeks, the annualized exacerbation rate in the budesonide/formoterol group was lower than in the as-needed albuterol group (absolute risk difference = 0.205; relative rate = 0.49; 95% CI, 0.33 to 0.72; number needed to treat = 5). The budesonide/formoterol group also had fewer severe exacerbations than the as-needed albuterol group (9 vs. 23; relative rate = 0.40; 95% CI, 0.18 to 0.86) and longer time to first exacerbation (hazard ratio = 0.46; 95% CI, 0.29 to 0.73). Symptom control scores measured by the Asthma Control Questionnaire (range = 0 to 6, with 6 indicating maximum impairment) were lower in the budesonide/formoterol group compared with the as-needed albuterol group (mean difference = −0.15; 95% CI, −0.24 to −0.06). The FEV_1 did not differ significantly between groups.

A 2018 RCT investigated the effectiveness and safety of ICS/LABAs as a reliever medication in 2,554 people 12 years and older with mild asthma.[2] Two of the three arms directly compared the effects of budesonide/formoterol (one inhalation as needed) plus twice-daily placebo (n = 1,279) with a terbutaline reliever (0.5 mg as needed from a pressurized metered dose inhaler) plus twice-daily placebo (n = 1,280). The study found that the budesonide/formoterol group had a greater mean percentage of weeks with well-controlled asthma than the terbutaline group (34% vs. 31% weeks; odds ratio = 1.14; 95% CI, 1.0 to 1.3; $P = .046$). Well-controlled asthma was defined as having a week with no nighttime awakenings due to asthma, with no additional inhaled or systemic corticosteroid use, and in which two or more of the following criteria were met: two or fewer days with a daily asthma score greater than 1; two or fewer days of as-needed medication use; or morning peak expiratory flow rate of 80% or greater of the predicted rate. Patients in the budesonide/formoterol group had a 64% lower rate of severe exacerbations (defined as worsening asthma leading to the use of systemic glucocorticoids for three days or greater, inpatient hospitalization, or an emergency department visit leading to the use of systemic glucocorticoids) than those in the terbutaline group (annualized exacerbation rate = 0.07 vs. 0.20; rate ratio = 0.36; 95% CI, 0.27 to 0.49) and a prolonged time to first severe exacerbation (hazard ratio = 0.44; 95% CI, 0.33 to 0.58). Adverse events, including upper respiratory tract infections, pharyngitis, and bronchitis, were more frequent in the terbutaline group than in the budesonide/formoterol group (43% vs. 38%; no *P* value provided), and more adverse events led to discontinuation in the terbutaline group than in the budesonide/formoterol group (2.9% vs. 0.8%).

A 2018 systematic review and meta-analysis of 16 RCTs involving 22,748 patients four to 75 years of age with persistent asthma studied the effectiveness of SMART (i.e., the use of an ICS/LABA combination as both controller and quick-relief therapy) on asthma outcomes. Results from the original group were compared with two additional regimens: (1) the same ICS/LABA dose as the original group for maintenance plus a SABA as needed for quick relief, and (2) a higher dose of the ICS/LABA than was used in the original group for maintenance plus a SABA as needed for quick relief.[3] Among people 12 years and older, SMART was associated with a decreased risk of severe asthma exacerbations (defined as use of systemic corticosteroids, hospitalization, emergency department visits, intensive care admission or intubation, or as otherwise defined by the study) compared with same-dose ICS/LABA (five trials; n = 8,473; risk ratio = 0.68; 95% CI, 0.58 to 0.80) and higher-dose ICS/LABA (two trials; n = 5,625; risk ratio = 0.77; 95% CI, 0.60 to 0.98). There were no significant associations between the use of SMART and the risk of mild asthma exacerbation, all-cause mortality, asthma symptom control as measured by the Asthma Control Questionnaire, or changes in FEV_1, forced vital capacity, or percentage of predicted FEV_1. Trial follow-ups ranged from six to 12 months and may be limited in the analysis of long-term outcomes. The results were not limited by heterogeneity (I^2 = 0% to 29%; $P > .10$).

Recommendations From Others

The Global Initiative for Asthma recommends against using SABAs alone and offers two tracks for treating asthma in adults and adolescents.[4] Using the preferred track 1, the reliever is given as needed using low-dose ICS/formoterol across the spectrum of asthma severity. In the alternative track 2, a SABA reliever is suggested when ICS/formoterol is unavailable or is not preferred by a patient at low risk of exacerbation.

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