Budesonide/formoterol or budesonide/albuterol as anti-inflammatory reliever therapy for asthma

Lipworth, Brian; Kuo, Chris RuiWen; Stewart, Kirsten; Chan, Rory

Published in:
Journal of Allergy and Clinical Immunology: In Practice

DOI:
10.1016/j.jaip.2024.02.003

Publication date:
2024

Budesonide/Formoterol or Budesonide/Albuterol as Anti-Inflammatory Reliever Therapy for Asthma

Brian Lipworth, MD, Chris RuiWen Kuo, MBChB, MD, Kirsten Stewart, MBChB, and Rory Chan, MBChB, PhD *Dundee, United Kingdom*

Overuse of reliever as short-acting beta-agonist and associated underuse of controller as inhaled corticosteroid (ICS) administered via separate inhalers results in worse asthma outcomes. Such discordance can be obviated by combining both controller and reliever in the same inhaler. So-called anti-inflammatory reliever (AIR) therapy comprises the use of a single inhaler containing an ICS such as budesonide (BUD) in conjunction with a reliever as either albuterol (ALB) or formoterol (FORM), to be used on demand, with variable dosing driven by asthma symptoms in a flexible patient-centered regimen. Global guidelines now support the use of BUD-ALB as AIR therapy to reduce exacerbations, either on its own in mild asthma or in conjunction with fixed-dose maintenance ICS-long-acting beta-agonist in moderate to severe asthma. Using BUD-FORM on its own allows patients to seamlessly move in an intuitive flexible fashion between AIR and maintenance and reliever therapy, by stepping up and down the dosing escalator across a spectrum of asthma severities. Head-to-head clinical studies are indicated to compare BUD-FORM versus BUD-ALB as AIR in mild asthma, and also BUD-FORM as maintenance and reliever therapy versus BUD-ALB as AIR plus maintenance ICS-long-acting beta-agonist in moderate to severe asthma. Patients should be encouraged to make an informed decision in conjunction with their health care professional regarding the best therapeutic option tailored to their individual needs, which in turn is likely to result in long-term compliance and associated optimal asthma control. **(J Allergy Clin Immunol Pract 2024;12:889-93)**

Key words: *Anti-inflammatory reliever; Asthma; Type 2 (T2) inflammation; Inhaled corticosteroid; Budesonide; Albuterol; Formoterol; Exacerbations*

RELATIONSHIP BETWEEN CONTROLLER AND RELIEVER THERAPY

The tenets of persistent asthma comprise type 2 (T2) inflammation, airway hyperresponsiveness (AHR), and reversibility of airflow obstruction. The inflammatory cascade in asthma is characterized by activation of T2 cytokines including IL-4, IL-5, and IL-13, predominantly involving influx of eosinophils and twitchy airway smooth muscle (ASM).[1] Thus, from first principles, the treatment of asthma should be to dampen down T2 inflammation, which in turn will result in attenuated ASM lability and associated AHR improvement.

Conventionally, pharmacotherapy for mild persistent asthma involves using short-acting beta-agonists (SABAs) such as albuterol (ALB) on demand as a fast- onset reliever acting on ASM along with a disease-modifying controller as low-dose inhaled corticosteroid (ICS) to suppress T2 inflammation.[2] Using SABA alone on demand without ICS is therefore no longer considered appropriate for mild persistent asthma. It is unrealistic for patients to remember to use their ICS every time they require rescue with SABA as concomitant separate inhalers, even though this is currently advocated as an option by global and US guidelines in mild asthma.

For patients with moderate to severe persistent asthma, the preferred option is usually maintenance fixed-dose combination inhaler therapy containing ICS with long-acting beta-agonist (ICS-LABA), which affords better control than ICS due to the stabilizing effect of ASM and attendant attenuation of AHR conferred by LABA.[2,3] Although there is a dose-response effect for reducing exacerbations and AHR with ICS,[4] the LABA moiety confers additional further reductions, albeit the greatest impact is due to the former.[5] Indeed, by acting on ASM, the LABA moiety will have a proportionately greater effect on symptoms and lung function than on exacerbations. A marginal further reduction in exacerbations may be conferred by adding in

Scottish Centre for Respiratory Research, School of Medicine, University of Dundee, Ninewells Hospital, Dundee, United Kingdom

Conflicts of interest: B. Lipworth reports nonfinancial support (equipment) from GlaxoSmithKline (GSK); grants, personal fees (consulting, talks, and advisory board), and other support (attending American Thoracic Society and European Respiratory Society [ERS] meetings) from AstraZeneca; personal fees (talks and consulting) from Sanofi; personal fees (consulting, talks, and advisory board) from Circassia in relation to the submitted work; grants, personal fees (consulting, talks, advisory board), and other support (attending ERS meetings) from Teva; personal fees (talks and consulting) and grants and other support (attending ERS and British Thoracic Society [BTS] meetings) from Chiesi; personal fees (consulting) from Lupin, Glenmark, Dr Reddy, and Sandoz; grants, personal fees (consulting, talks, and advisory board), and other support (attending BTS meetings) from Boehringer Ingelheim; grants and personal fees (advisory board and talks) from Mylan outside of the submitted work; and that his son is presently an employee of AstraZeneca. C. R. Kuo reports personal fees from AstraZeneca and Chiesi, and nonfinancial support from GSK outside the submitted work. K. Stewart reports no conflicts of interest. R. Chan reports personal fees (talks) and support attending ERS meetings from AstraZeneca, personal fees (consulting) from Vitalograph, and personal fees (talks) from Thorasys.

Received for publication January 9, 2024; revised January 31, 2024; accepted for publication February 1, 2024.

Available online February 10, 2024.

Corresponding author: Brian Lipworth, MD, Scottish Centre for Respiratory Research, School of Medicine, University of Dundee, Ninewells Hospital, Dundee DD1 9SY, United Kingdom. E-mail: b.j.lipworth@dundee.ac.uk.

2213-2198

https://doi.org/10.1016/j.jaip.2024.02.003

Abbreviations used
AHR- airway hyperresponsiveness
AIR- anti-inflammatory reliever
ALB- albuterol
ASM- airway smooth muscle
BUD- budesonide
FDA- Food and Drug Administration
FORM- formoterol
ICS- inhaled corticosteroid
LABA- long-acting beta-agonist
MART- maintenance and reliever therapy
pMDI- pressurized metered dose inhaler
SABA- short-acting beta-agonist
T2- type 2

long-acting muscarinic antagonist, although the evidence for such additivity in patients taking high-dose ICS-LABA is unconvincing.[6]

In reality, patients often overuse their SABA and become overreliant as they perceive the symptomatic benefit of its rapid onset by improvements in airway caliber, in contrast to often underusing their ICS-containing medication. This in turn results in relative discordance between use of ICS-containing inhalers and SABA reliever, which can lead to poor control with associated exacerbations and even death.[7-10]

PRINCIPLES UNDERLYING AIR THERAPY

To ensure perfect concordance between ICS and reliever, therapeutic strategies have been developed whereby both drug components are contained in the same inhaler, also known as anti-inflammatory reliever (AIR) therapy.[11] Such AIR may contain low-dose ICS as budesonide (BUD) along with a fast-onset LABA as formoterol (FORM) or with SABA as ALB. Using an AIR regimen means that every time the patient requires their reliever, they receive an enforced dose of controller ICS, thereby suppressing the underlying T2 inflammation. The premise here is that patients will effectively self-adjust their ICS dose against symptoms, thereby improving control and preventing breakthrough asthma flare ups. When using BUD-FORM as a reliever, patients may seamlessly step up and down the dose escalator between AIR and maintenance and reliever therapy (MART) using the same inhaler over a range of asthma severity (Figure 1).[11] One study in mild asthma found that use of beclomethasone dipropionate 250 μg with ALB 100 μg as a single reliever inhaler was as effective as maintenance beclomethasone dipropionate 250 μg twice daily with separate rescue ALB, along with lower ICS exposure.[12]

The Food and Drug Administration (FDA) has approved BUD-FORM (160/4.5 μg) pressurized metered dose inhaler (pMDI) only for regular fixed-dose maintenance use but not as AIR or MART in the United States, although it is approved for this indication in many other countries via dry powder inhaler for those 12 years and older at up to 12 puffs daily. Having said that, the most recent US guidelines advocate for the use of low-dose BUD-FM as MART at steps 3/4 for moderate asthma.[13] The FDA indication statement for BUD-ALB 80/90 μg pMDI is rather vague for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma aged 18 years and older. This might be interpreted as meaning that BUD-ALB may be used as reliever therapy across a range of asthma severity, but only in persistent asthma where maintenance therapy is also needed. Global and US guidelines advocate for ICS and ALB to be used concomitantly as separate inhalers as needed in step 2 for mild intermittent or persistent asthma. Strictly speaking, because BUD-ALB is not FDA approved for maintenance use, it should not be used on its own for mild persistent asthma at step 2 in United States, although from a pragmatic perspective it may not be possible to clearly distinguish between intermittent and persistent mild asthma per se. The BUD-ALB 80/90 μg pMDI formulation is taken as 2 actuations as reliever used up to a maximum of 12 puffs in 24 hours. Taking this literally, for example, in a patient with mild asthma who takes on average between 6 and 12 puffs daily of BUD-ALB as their sole inhaler, using AIR would therefore effectively equate to it being used as MART. One potential issue is that patients may be prescribed 2 different devices, for example, a dry powder inhaler for ICS-LABA plus BUD-ALB via pMDI, which could lead to complicating issues with inhaler technique, even though this would be no different to ALB via pMDI as rescue therapy. Ideally, one might advocate for the controller and reliever to be used via the same device, both being delivered via pMDI plus spacer to optimize lung deposition and obviate issues with coordination and local ICS dose-related adverse effects.

We would suggest that patients with moderate to severe persistent asthma taking maintenance ICS combination therapy but also requiring on a regular basis 4 or more puffs daily of additional BUD-ALB reliever, along with poor control as an asthma control questionnaire score of 1.5 or more and a severe exacerbation, should be promptly referred on to specialist care. Such evaluation might include optimizing the dose of maintenance ICS controller, checking controller adherence and inhaler technique, performing spirometry, measuring T2 biomarkers and relevant autoantibodies, identifying trigger factors such as allergens and occupational chemicals, looking for comorbidities such as nasal polyps, bronchiectasis, eosinophilic granulomatosis with polyangiitis, or esophageal reflux, as well as considering performing high-resolution computed tomography of chest and sinuses.

From a pharmacological perspective, there is clinically relevant synergy between the moieties in terms of the rapid reversal by BUD on airway beta-2 receptor downregulation and subsensitivity induced by FORM.[14] Moreover, in patients taking regular fixed-dose ICS-LABA, cross-tolerance may develop in terms of blunting of ALB response when used as reliever therapy in the presence of acute bronchoconstriction as might occur in the setting of acute asthma.[15-17] It is unclear whether this phenomenon might be obviated by using BUD-ALB in terms of a facilitatory effect of BUD on airway beta-2 receptors.[18] Reassuringly, it is also worth noting that a bolus of systemic corticosteroid rapidly reverses beta-2 receptor downregulation and restores airway bronchodilator responsiveness in patients with asthma taking regular ICS-FORM.[19]

BUDESONIDE-FORMOTEROL RELIEVER

The phase 3 trial evidence with BUD-FORM (160/4.5 μg) as AIR for mild asthma is compelling in terms of clear superiority of control compared with SABA alone.[11] Moreover, using BUD-FORM AIR versus regular fixed low-dose BUD plus SABA on demand in mild asthma shows noninferiority for disease control

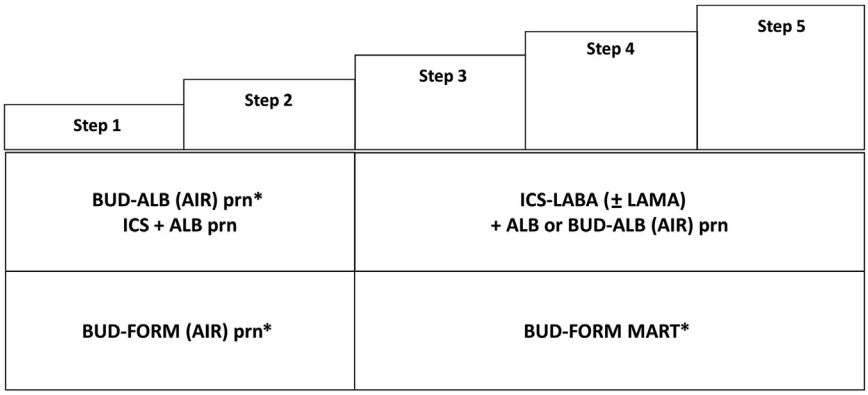

FIGURE 1. Schematic illustration of simplified global guidelines incorporating AIR therapy as needed (*pro re nata* [prn]) with BUD-FORM (160/4.5 μg per actuation) for mild asthma (step 1/2), stepping up and down as MART between 2 and 12 actuations daily for moderate to severe asthma (step 3/4/5). BUD-ALB (80/90 μg per actuation) as AIR (prn) between 2 and 12 actuations daily either alone (step 1/2) in mild asthma or in conjunction with fixed-dose maintenance therapy comprising low-medium-high-dose ICS-LABA as single-inhaler dual or triple therapy with long-acting muscarinic antagonist (ICS-LABA-LAMA), for moderate to severe asthma (step 3/4/5). *BUD-ALB is not presently approved outside of the United States. BUD-ALB is not approved in the United States by FDA as maintenance therapy including for mild persistent asthma at step 2. Alternatively, separate ICS and ALB inhalers are approved for concomitant on-demand use by US and global guidelines at step 2. BUD-FORM is not approved in the United States by FDA for either AIR or MART but is approved as such in other countries.

along with lower overall ICS exposure.[11] BUD-FORM when used as MART in moderate to severe asthma also produces better control and an associated lower ICS burden compared with fixed-dose maintenance ICS-LABA plus SABA.[20] At present, beclomethasone dipropionate/formoterol 100/6 μg combination as pMDI or dry powder inhaler only has an indication for MART in persistent asthma as 2 to 8 actuations daily in those aged 18 years and above, albeit in real-life, patients often intuitively step down to AIR of their own volition.

Although AIR therapy with BUD-FORM is only indicated for mild asthma, in reality, this distinction is somewhat artificial because mild to moderate asthma is a continual spectrum of disease determined by prevailing extrinsic trigger factors. For example, an individual may have moderate asthma in response to seasonal allergic or viral triggers but for the rest of the year they have mild asthma. Thus, a more pragmatic approach using AIR allows patients to always be taking an optimized dose of ICS, which is matched to the degree of T2 inflammation by escalating and de-escalating the number of actuations between reliever and plus or minus maintenance use[11] (Figure 1). This is in contrast to always having to take a fixed dose of ICS or ICS-LABA whether the patient needs it or not. In other words, BUD-FORM via AIR-MART is a more patient-centered, intuitive flexible regimen for controlling persistent asthma with a single inhaler. This is reflected in current global guidelines whereby there are 2 possible tracks for mild to moderate asthma: one suggesting fixed-dose maintenance ICS or ICS-LABA along with ALB or BUD-ALB reliever as needed, and the other route whereby BUD-FORM alone is the preferred reliever used along a continuum with AIR or MART[2] (Figure 1). Clearly, this approach requires detailed input from health care professionals to educate patients regarding the principles of AIR-MART in relation to disease control and what to do during an exacerbation. In our asthma clinic, we approach this by telling patients with persistent asthma the simple axiom when using BUD/FORM 160/4.5 μg as AIR-MART "use more puffs when you need it and less when you don't," with the caveat of not exceeding the maximum permitted number of actuations amounting to 12 per day.[21] This in turn begs the pertinent question as to whether BUD-FORM can be used as AIR-MART to reduce the ICS burden in the presence of biologic therapy to target eosinophil-driven exacerbations. In the SHAMAL study, in severe eosinophilic asthma in patients who were identified as being benralizumab superresponders, the use of BUD-FORM as AIR-MART compared with maintenance therapy was associated with successful tapering of ICS dose with the variable-dosing regimen, although it was associated with a small degree of worsening of lung function and fractional exhaled nitric oxide escape, in the absence of increased exacerbations.[22]

BUD-ALB reliever

The key phase 3 trial supporting BUD-ALB (80/90 μg per actuation) as reliever therapy was from the MANDALA trial where, for the primary end point, there was a 26% relative reduction in the risk of first severe exacerbation compared with ALB (90 μg per actuation) alone, both used for a minimum of 24 weeks as 2 puffs of reliever therapy in patients with uncontrolled moderate to severe asthma receiving a range of maintenance ICS-LABA combination doses.[23] To put this into context comparing BUD-ALB versus ALB with regard to absolute exacerbations, the number needed to treat was 12.5 to prevent an exacerbation, and it would take on average 6.7 years to prevent an exacerbation in a given individual. The use of BUD-ALB was also accompanied by lower systemic corticosteroid exposure. A clinically meaningful reduction in asthma control questionnaire score (>0.5) occurred in 6.7% more cases for BUD-ALB versus ALB and the mean dose of BUD-ALB used was 2.6 inhalations daily and 2.8 with ALB. Hence, it appears that patients were effectively taking a higher maintenance dose of ICS with additional use of BUD-ALB, which led to better outcomes. Notably, only 27% of the

patients were receiving high-dose ICS-LABA at baseline, while the presence of a mean FEV_1 of 64% predicted and reversibility of 28% indicates that there was likely to be considerable room for improvement. This begs the pertinent question as to whether BUD-ALB reliever would have been as effective in patients whose maintenance ICS-LABA dose had been sufficiently adapted during the initial run-in period, perhaps with the use of fractional exhaled nitric oxide or blood eosinophils to guide optimal suppression of T2 inflammation.[24] Furthermore, there was no check on adherence to the background ICS-LABA therapy such that it is conceivable BUD-ALB might have been relatively more effective in individuals who were noncompliant on maintenance ICS-LABA. One could cogently argue that for patients who have discordance between controller and reliever medications, using BUD-ALB would provide a safety net if they become overreliant on their reliever.

The DENALI study in patients with poorly controlled mild to moderate asthma was FDA mandated to demonstrate the relative efficacy of both components with regular BUD-ALB. There were 5 randomized treatment arms each comprising 2 actuations 4 times daily over 12 weeks with BUD 80 μg, BUD-ALB 40/90 μg, 80/90 μg, ALB 90 μg, or placebo. There were significant improvements with BUD-ALB 80/90 μg compared with ALB 90 μg for the coprimary end points of peak and trough FEV_1 along with significantly greater reductions in asthma control questionnaire score and fewer exacerbations.[25] Adherence to trial inhalers was 94%, which would not be in keeping with real-life use, while the regular 4-times daily regimen does not reflect the indication as reliever therapy. The FEV_1 time profile response on day 1 would be more akin to reliever use and showed no clinically relevant difference between 2 puffs of BUD-ALB 80/90 μg and ALB 90 μg. Pointedly, only 47% of patients were taking ICS at baseline such that patients were not being optimally treated before enrollment. This study does not support the use of BUD-ALB compared with ALB when used alone as AIR in mild asthma, although one might predict it would be superior based on data comparing beclomethasone dipropionate-ALB versus ALB alone.[12] A study will compare BUD-ALB to ALB in mild asthma in terms of acute reliever use after mannitol-induced bronchoconstriction (NCT05555290). Another trial (NCT05505734) will compare BUD-ALB to ALB in mild asthma used as AIR powered on time to first severe exacerbation. There are no data that have compared head-to-head BUD/ALB versus BUD-FORM as sole reliever therapy in mild asthma. From first principles, a cogent case could be made for superiority with BUD/FM versus BUD/ALB due to better stabilization of FM versus ALB on ASM, which would lead to fewer exacerbations. Also, we would be interested to see a trial in moderate to severe asthma comparing BUD-ALB as reliever plus maintenance ICS-LABA against BUD-FORM as MART.

THE WAY FORWARD

If both formulations of BUD-ALB and BUD-FORM were approved as AIR, aside from cost issues, presumably prescribers might opt for the latter given the known superiority of the LABA moiety in terms of improving disease control as well as the convenience of the longer duration of response. Pointedly, BUD-FORM also offers the possibility of seamlessly moving in a flexible fashion between AIR and MART regimens across a range of asthma severity (Figure 1). It is important to acknowledge that the BUD-ALB is considerably more expensive than ALB such that patients and payers alike may be deterred from using it, despite better outcomes with the former. The availability of generic formulations of BUD-FORM might also reduce the cost for this particular combination inhaler. For patients with uncontrolled persistent asthma, clinicians may wish to address the simple things first. This might include checking inhaler technique and device preference, address relevant triggers, in addition to optimizing the dose of ICS-containing maintenance therapy using T2 biomarkers.[26] Ultimately, patients should be able to make an informed decision along with their health care professional regarding the best option tailored to their individual needs, because that is likely to result in optimal long-term compliance and associated asthma control.

REFERENCES

1. Porsbjerg C, Melen E, Lehtimaki L, Shaw D. Asthma. Lancet 2023;401:858-73.
2. Levy ML, Bacharier LB, Bateman E, Boulet LP, Brightling C, Buhl R, et al. Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update. NPJ Prim Care Respir Med 2023;33:7.
3. Currie GP, Jackson CM, Ogston SA, Lipworth BJ. Airway-stabilizing effect of long-acting beta2-agonists as add-on therapy to inhaled corticosteroids. QJM 2003;96:435-40.
4. Currie GP, Fowler SJ, Lipworth BJ. Dose response of inhaled corticosteroids on bronchial hyperresponsiveness: a meta-analysis. Ann Allergy Asthma Immunol 2003;90:194-8.
5. Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group [see comment] [erratum appears in N Engl J Med 1998;338:139]. N Engl J Med 1997;337:1405-11.
6. Lipworth B, Stewart KE, Chan R. Pragmatic reappraisal of long-acting muscarinic antagonists at steps 4 and 5 for persistent adult asthma. Ann Allergy Asthma Immunol 2022;129:274-5.
7. Gonem S, Cumella A, Richardson M. Asthma admission rates and patterns of salbutamol and inhaled corticosteroid prescribing in England from 2013 to 2017. Thorax 2019;74:705-6.
8. Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockroft D, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. Am J Respir Crit Care Med 1994;149:604-10.
9. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000;343:332-6.
10. Bloom CI, Cabrera C, Arnetorp S, Coulton K, Nan C, van der Valk RJP, et al. Asthma-related health outcomes associated with short-acting beta(2)-agonist inhaler use: an observational UK study as part of the SABINA Global Program. Adv Ther 2020;37:4190-208.
11. Lipworth B, Chan R, Kuo CR. Anti-inflammatory reliever therapy for asthma. Ann Allergy Asthma Immunol 2020;124:13-5.
12. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med 2007;356:2040-52.
13. Chipps BE, Murphy KR, Oppenheimer J. 2020 NAEPP Guidelines Update and GINA 2021-Asthma Care Differences, Overlap, and Challenges. J Allergy Clin Immunol Pract 2022;10:S19-30.
14. Aziz I, Lipworth BJ. A bolus of inhaled budesonide rapidly reverses airway subsensitivity and beta2-adrenoceptor down-regulation after regular inhaled formoterol. Chest 1999;115:623-8.
15. Lee DK, Jackson CM, Currie GP, Cockburn WJ, Lipworth BJ. Comparison of combination inhalers vs inhaled corticosteroids alone in moderate persistent asthma. Br J Clin Pharmacol 2003;56:494-500.
16. Lipworth BJ, Aziz I. A high dose of albuterol does not overcome bronchoprotective subsensitivity in asthmatic subjects receiving regular salmeterol or formoterol. J Allergy Clin Immunol 1999;103:88-92.
17. Lee D, Jackson C, Bates C, Lipworth B. Cross tolerance to salbutamol occurs independently of β2 adrenoceptor genotype-16 in asthmatic patients receiving regular formoterol or salmeterol. Thorax 2004;59:662-7.
18. Cockcroft DW, Swystun VA, Bhagat R. Interaction of inhaled beta 2 agonist and inhaled corticosteroid on airway responsiveness to allergen and methacholine. Am J Respir Crit Care Med 1995;152:1485-9.

19. Tan KS, Grove A, McLean A, Gnosspelius Y, Hall IP, Lipworth BJ. Systemic corticosteriod rapidly reverses bronchodilator subsensitivity induced by formoterol in asthmatic patients. Am J Respir Crit Care Med 1997;156:28-35.
20. Beasley R, Bruce P, Houghton C, Hatter L. The ICS/formoterol reliever therapy regimen in asthma: a review. J Allergy Clin Immunol Pract 2023;11:762-772.e1.
21. Lipworth B, Kuo CR, Chan R. Making simple things complicated using anti-inflammatory reliever therapy. Eur Respir J 2020;55:2000267.
22. Jackson DJ, Heaney LG, Humbert M, Kent BD, Shavit A, Hiljemark L, et al. Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study. Lancet 2024;403:271-81.
23. Papi A, Chipps BE, Beasley R, Panettieri RA Jr, Israel E, Cooper M, et al. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. N Engl J Med 2022;386:2071-83.
24. Lipworth BJ, Chan R, Stewart KE. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. N Engl J Med 2022;387:662-3.
25. Chipps BE, Israel E, Beasley R, Panettieri RA Jr, Albers FC, Rees R, et al. Albuterol-budesonide pressurized metered dose inhaler in patients with mild-to-moderate asthma: results of the DENALI double-blind randomized controlled trial. Chest 2023;164:585-95.
26. Anderson WJ, Short PM, Jabbal S, Lipworth BJ. Inhaled corticosteroid dose response in asthma: should we measure inflammation? Ann Allergy Asthma Immunol 2017;118:179-85.