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REVIEW

New Versus Old: The Impact of Changing Patterns of Inhaled Corticosteroid Prescribing and Dosing Regimens in Asthma Management

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ABSTRACT

Inhaled corticosteroid (ICS)-containing therapies are the mainstay of pharmacological management of asthma. They can be administered alone or in combination with a long-acting bronchodilator, depending on asthma severity, and may also be supplemented with short-acting bronchodilators for as-needed rescue medication. Adherence to asthma therapies is generally poor and characterized by underuse of ICS therapies and over-reliance on short-acting bronchodilators, which leads to poor clinical outcomes. This article reviews efficacy versus systemic activity profiles for various dosing regimens of budesonide (BUD) and fluticasone propionate (FP). We performed a structured literature review of BUD and FP regular daily dosing, and BUD/formoterol (FOR) as-needed dosing, to explore the relationship between various dosing patterns of ICS regimens and the risk–benefit profile in terms of the extent of bronchoprotection and cortisol suppression. In addition, we explored how adherence could potentially affect the risk–benefit profile, in patients with mild, moderate, and moderate-to-severe asthma. With a specific focus on BUD or FP-containing treatments, we found that regular

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daily ICS and ICS/long-acting β_2-agonist (LABA) dosing had a greater degree of bronchoprotection than as-needed BUD/FOR dosing or BUD/FOR maintenance and reliever therapy (MART) dosing, and still maintained low systemic activity. We also found that the benefits of regular daily ICS dosing regimens were diminished when adherence was low (50%); the shorter duration of bronchoprotection observed was similar to that seen with typical as-needed BUD/FOR usage. These findings have implications for aiding clinicians with selecting the most suitable treatment option for asthma management, and subsequent implications for the advice clinicians give their patients.

Keywords: As-needed dosing; Asthma; Fluticasone propionate; Inhaled corticosteroid; Regular maintenance dosing; Risk benefit; Budesonide; Bronchoprotection; Systemic effects

PLAIN LANGUAGE SUMMARY

Inhaled corticosteroid (ICS)-containing therapies can be administered in a variety of ways depending on a patient's asthma severity. Patients with mild asthma tend to experience symptom relief with as-needed or regular daily use of an ICS alone, whereas patients with more severe asthma may require regular daily use of an ICS plus a long-acting β_2-agonist (LABA) to experience sufficient asthma control. However, failure to correctly adhere to ICS-containing therapies or an over-reliance on short-acting bronchodilators for symptom relief hinders optimal asthma management, thus negatively affecting overall patient health and wellbeing. Understanding how different dosing regimens affect the degree of bronchoprotection (efficacy) and cortisol suppression (systemic activity) of ICS treatments would benefit physicians by helping them to prescribe the most appropriate treatment for their patient's asthma. We performed a structured literature review of two ICS molecules—budesonide (BUD) (alone and combined with formoterol [FOR]) and fluticasone propionate (FP)—to explore the relationship between various ICS dosing regimens, and then used these findings to construct models for ICS risk–benefit profiles. Our models factored in different ICS dosing regimens—as-needed, regular daily dosing, and maintenance and reliever therapy (MART)—and various degrees of treatment adherence. We found that regular daily ICS and ICS/LABA dosing provided better bronchoprotection than as-needed BUD/FOR dosing or BUD/FOR MART dosing, but this benefit was diminished with low adherence. Regular daily dosing maintained low cortisol suppression, which indicated a fairly low risk of negative side effects. Our findings have subsequent implications for optimizing treatment in patients with asthma.

Key Summary Points

Why carry out this study?

There are very few studies that compare efficacy of available treatment regimens for mild to moderate asthma based on airway efficacy/systemic activity profiles.

We investigated whether regular versus flexible inhaled corticosteroid (ICS) dosing had different airway efficacy and systemic activity when administered to patients with mild, moderate, and moderate-to-severe asthma.

What was learned from the study?

Regular daily ICS or ICS/long-acting β_2-agonist (LABA) dosing regimens with budesonide (BUD) or fluticasone propionate had higher airway efficacy with similarly low systemic activity compared with as-needed BUD/formoterol (FOR) dosing in mild asthma, and maintenance and reliever therapy (MART) dosing in moderate and moderate-to-severe asthma, respectively.

Flexible dosing regimens (BUD/FOR as-needed or MART dosing) may not be the optimal pharmacological approach to manage all patients with asthma in clinical practice, and regular proactive dosing with ICS or ICS/LABA is more likely to deliver an optimal dose for controlling underlying airway inflammation.

These findings have implications for clinicians choosing treatment options for the management of asthma, and the advice they give to their patients.

INTRODUCTION

Asthma is a chronic disease that is characterized by respiratory symptoms such as wheeze, chest tightness, and airflow limitation, and which is associated with airway hyperresponsiveness and inflammation [1]. Inhaled corticosteroid (ICS)-containing therapies are the mainstay of pharmacological asthma management: these can be administered alone or in combination with a long-acting bronchodilator depending on asthma severity, and may also be supplemented with short-acting bronchodilators for rescue medication as needed [1]. Adherence to asthma therapies is generally poor and characterized by underuse of ICS therapies and over-reliance on short-acting bronchodilators, leading to poor clinical outcomes [2]. Patients tend to have a low perceived need for asthma medications and communication between physicians and patients is not optimal: today, asthma is treated "as needed" by patients themselves which contributes to a lack of understanding of the disease and, as a result, leads to poor adherence and suboptimal asthma control.

A core feature of asthma leading to the manifestation of symptoms is the underlying airway inflammation [1], and it is well documented that failure to adequately treat this inflammation is likely to worsen asthma symptoms and increase exacerbation risk [3, 4]. The anti-inflammatory efficacy of ICS molecules is determined not only by their glucocorticoid receptor binding affinity but also by their pharmacokinetic (PK), pharmacodynamic (PD), and physicochemical properties, and on the administered dose [5, 6]. Together, these factors can influence the extent and duration of treatment efficacy and the extent of unwanted systemic activity, and can also lead to differences in the risk–benefit profile of ICS dose regimens, particularly where regular daily maintenance therapy is deviated from—i.e., when adherence is poor or when as-needed dosing is adopted as an alternative to regular daily dosing [7]. Although some studies have compared regular daily dosing with as-needed regimens in the management of asthma [8–11], further investigation is needed to determine the relative risk–benefit of these ICS dose regimens options for various treatment outcomes.

Ideally, the prescribed dose regimen for any ICS or ICS-containing therapy should meet at least the minimum dose required for effective treatment and not exceed the upper dose threshold for high risk of systemic adverse effects. Keeping the dose of an ICS treatment within this range ensures that therapeutic effects (including a reduction in airway hyperresponsiveness and corresponding bronchoprotective effect) are maximized and risks of the potential for systemic side effects are minimized [12]. Thus, it is important for prescribers to understand how various ICS use patterns impact the ability to achieve clinical control and minimize the risk of unwanted systemic effects to optimize patient care.

The risk–benefit profiles of different regular daily ICS dosing regimens of budesonide (BUD), fluticasone propionate (FP), and fluticasone furoate in patients with asthma have been previously investigated [12]. Building upon these findings, we now report an analysis of efficacy versus systemic activity profiles for various dosing regimens of BUD and FP. First, we performed a structured literature review of BUD and FP regular daily dosing, and BUD/FOR as-needed dosing, to evaluate the dosing range seen in clinical studies of patients with mild asthma. We also used selected ICS/long-acting β_2-agonist (LABA) combination therapies, including regular twice-daily ICS/LABA, and

BUD/formoterol (FOR) maintenance and reliever therapy (MART) dosing data in clinical studies of patients with moderate-to-severe asthma. Finally, using the actual patterns of ICS use data collected from the structured literature review, and other ICS use scenarios of interest, we used previously validated and published PK/PD modeling/simulation methodology [7] to simulate airway efficacy and systemic activity for these ICS dosing regimens in mild and moderate-to-severe asthma.

METHODS

Literature Review Search Strategy and Selection Criteria

PubMed was searched for articles that were published between 1 January 2000 and 27 April 2021. Publications were included at initial title search if they met pre-defined criteria, namely: an adult/adolescent study population (≥ 12 years old); twice-daily (BID), as-needed, and/or MART dosing in mild and/or moderate or moderate-to-severe persistent asthma; an appropriate study design was used (i.e., randomized controlled trials [RCTs], real-world data [RWD] or observational trials, meta-analyses, and systematic literature reviews).

Publications with titles describing studies of patients with moderate-to-severe asthma were also included for further review and analysis. Published studies that analyzed BUD and FP were selected because BUD and FP are the most widely used ICS molecules (alone or in combination with a LABA/muscarinic antagonist) worldwide, and because they can both be prescribed for treating asthma [13, 14]. The BUD/FOR MART dosing approach has limited data in children and so we did not include pediatric studies in our analysis. All inclusion and exclusion criteria for the initial title search are provided in Fig. 1.

One reviewer screened all titles and abstracts of potential interest for full-text review and data extraction; per structured literature search methodology, 20% of these articles were chosen by a random sequence generator for review by a second reviewer, and in the event of any disagreement about which of these articles should be included, both reviewers further discussed to reach a consensus. Articles agreed by the reviewers for inclusion in the literature review (including the 20% of articles reviewed by two reviewers and the remaining 80% of articles reviewed by one reviewer) were then subjected to full-text review, and suitable articles from the full-text review were subsequently used for data extraction and analysis.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Literature Review Data Extraction and Analysis

Articles selected for data extraction were categorized into two groups according to the asthma severity reported: mild and mild-to-moderate asthma, or moderate and moderate-to-severe asthma. Data on ICS dose (including dose range and total, median, and mean daily dose) and use (including number of puffs/day and days' use of ICS) were collected from all publications. No data on inhaler type were collected.

Simulation of Outcomes for Various ICS Use Scenarios

Eligible publications identified in our literature review, from which the actual dose of ICS could be estimated from the available data, were used to simulate the extent and duration of airway efficacy and systemic activity for each ICS dose regimen of interest using previously validated and published PK/PD modeling and simulation methodology [7]. In addition to simulating the outcome for ICS use patterns documented in published studies, we also simulated the airway efficacy and systemic activity for regular daily and as-needed ICS dosing in mild asthma, and investigated the impact of 50%, 70%, and 100% adherence for BUD and FP regular daily doses (these values are in line with reports of ICS adherence in patients with asthma of 22–63% in the literature [8, 15, 16]). For the mild asthma

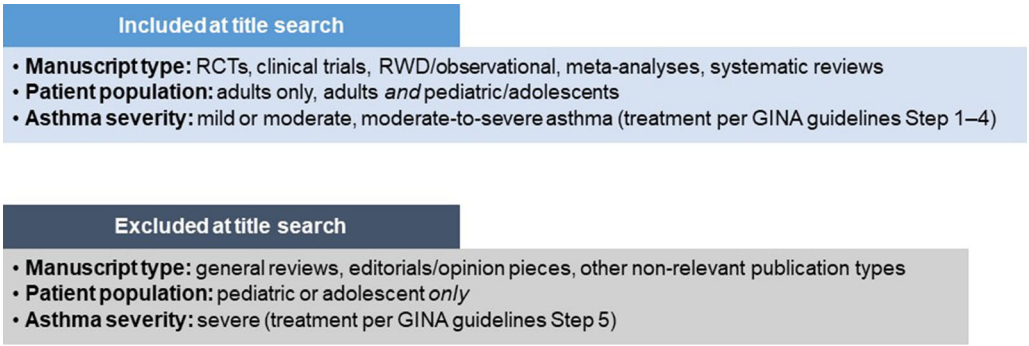

Fig. 1 Inclusion/exclusion criteria for literature search. *GINA* Global Initiative for Asthma, *RCT* randomized controlled trial, *RWD* real-world data

simulations, the efficacy endpoint was the percentage of time (hours) during 28 days of treatment when there was clinically significant bronchoprotection that would equate to a ≥ 1.0 doubling dose difference [1] from placebo in an adenosine monophosphate (AMP) challenge test [17]. These simulations assumed 3–4 ICS doses per week equated to as-needed ICS use, based on the reported average use of as-needed BUD/FOR in randomized trials of mild asthma [8, 11]. The simulation of airway efficacy and systemic activity with regular ICS/LABA daily dosing and BUD/FOR MART dosing in moderate and moderate-to-severe asthma was split into two parts and investigated 85% and 100% adherence scenarios for ICS alone or ICS/LABA combinations containing BUD and FP as ICS used in regular daily doses. For these clinical trials, where we simulated the outcomes in terms of bronchoprotection and systemic activity, it was possible to estimate the total ICS dose administered but not necessarily how this dose was taken by the participants, in terms of the split between maintenance and reliever doses. Since it is unlikely that adherence to the maintenance regimen was 100% (based on information available in published studies [7–11]), we also investigated an 85% adherence scenario assuming that this was a more feasible usage pattern among patients with asthma. For moderate and moderate-to-severe asthma simulations, a higher threshold for clinically significant bronchoprotection (≥ 1.5 and ≥ 2.0 doubling dose difference, respectively) was used on the assumption that higher ICS doses/bronchoprotective effects are required than in mild asthma. For BUD/FOR MART dosing, simulations of the pattern of usage were based on the number of puffs/day reported in the included studies (ranging from 1.03 to 1.83 as-needed BUD/FOR puffs/day and 2.7–5.0 total puffs/day). Airway efficacy was plotted as the percentage of time (hours) in 28 days of treatment when clinically significant bronchoprotection was achieved or exceeded: when this occurred for $\geq 70\%$ of the time bronchoprotection was considered high, and for $< 70\%$ of the time bronchoprotection was considered low. The threshold of 70% (i.e., the duration of clinically significant bronchoprotection with ≥ 1.0, ≥ 1.5, or ≥ 2.0 doubling dose during 28 days dosing) was based on the observation that dose regimens known to be efficacious in mild, moderate, and moderate-to-severe asthma achieve at least this extent of efficacy in the simulations when adherence is high, namely BUD 200 μg BID, FP 250 μg BID, and BUD 400 μg BID, respectively. For all doubling dose scenarios, mean (95% confidence interval) time during 28 days when bronchoprotection met or exceeded the doubling dose threshold was calculated. Systemic activity as a measure of safety was estimated as the average percentage of cortisol suppression (%) during a 28-day period: a dosing regimen where cortisol suppression was $< 20\%$ was considered to have low systemic activity. This threshold of 20% reduction in serum cortisol was used as a measure of safety; although a 20% reduction in serum cortisol seems small and not intrinsically associated

with adverse effects, it is close to the boundary of detectable systemic exposure for an exogenous corticosteroid and was therefore used as the cut-off above which a wider range of adverse effects became more likely [6]. Dosing regimens were assigned to one of four cohorts as follows: low airway efficacy/low systemic activity; low airway efficacy/high systemic activity; high airway efficacy/low systemic activity; high airway efficacy/high systemic activity. Treatments falling within the high airway efficacy/low systemic activity cohort would be considered as providing the optimal risk–benefit ratio.

RESULTS

Literature Search Summary

A complete study flow diagram is shown in Fig. 2. The initial search included 743 publications in total: this comprised 731 PubMed database hits and 34 key publications that were pre-identified by authors ahead of conducting the literature search. Twenty-two of these pre-identified key publications were captured in the initial literature search; the remaining 12 pre-identified key publications were added manually and included in the title and abstract screen. Full details of the PubMed search history and literature review criteria are provided in Supplementary Table S1.

Of the initial 743 publications identified, 269 articles (comprising irrelevant publication types, non-English articles, pediatric/adolescent-only populations [based on title], and severe and moderate-to-severe disease only [based on title]) were excluded at initial title screen, leaving 474 articles for title and abstract screen. A further 428 articles were excluded following title and abstract screening, leaving 46 articles for full-text review and data extraction (including 17 of the 34 pre-identified key publications).

Publications reporting on patients with mild or mild-to-moderate asthma included articles with treatment arms for BUD or FP BID regular dosing plus as-needed short-acting β_2-agonist (SABA), and/or BUD/FOR as-needed dosing. Publications reporting on patients with moderate or moderate-to-severe asthma included articles with treatment arms for BUD/FOR and FP/salmeterol (SAL) BID regular dosing, and/or BUD/FOR MART dosing. During full-text review, one article was excluded because it had once-daily FP dosing in both treatment arms, and the remaining 45 articles were retained for full-text data extraction. Thirty publications [8–11, 18–43] were grouped according to asthma severity (mild asthma [n = 9]; moderate asthma [n = 21]), and 15 publications [12, 44–57] were consulted in the development of the discussion section. Dosing data from 11 publications where the actual dose of ICS could be estimated [8–11, 21, 25, 29, 30, 34, 40, 43] (Table 1) were used as inputs to simulate outcomes.

ICS Airway Efficacy and Systemic Activity in Mild Asthma

The ICS dose and ICS use data that were extracted from publications in the mild asthma simulations are detailed in Table 2.

In the mild asthma simulations with $\geq$ 1.0 doubling dose efficacy threshold, all studies of interest fell into either the low airway efficacy/low systemic activity or high airway efficacy/low systemic activity quadrant, and regular daily dosing consistently offered a higher degree of bronchoprotection than as-needed dosing (Fig. 3). All final data from the mild asthma simulations are provided in Supplementary Table S2.

Regular daily BUD dosing arms from two clinical trials SYGMA-2 and Novel START [8, 9] fell within the low airway efficacy/low systemic activity quadrant, with 56.9% and 58.5% bronchoprotection and 10.2% and 10.5% cortisol suppression, respectively. The total 28-day ICS dose was 6000 μg and 6200 μg for SYGMA-2 and Novel START, respectively.

As-needed BUD dosing arms from three clinical trials (SYGMA-1, SYGMA-2, and Novel START) [8, 9, 11], and the simulations for irregular BUD and FP dosing (3–4 times per week) also fell in the low airway efficacy/low systemic activity quadrant, with bronchoprotection ranging from 24.3% to 28.1% and

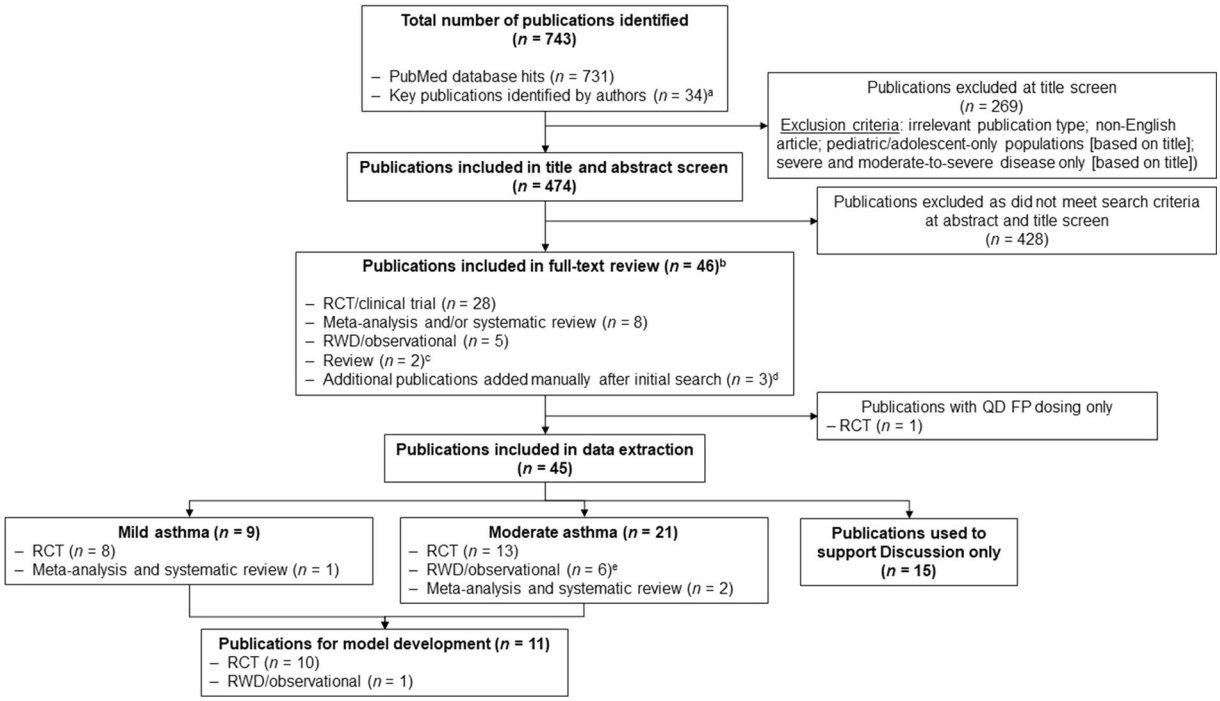

Fig. 2 Study flow diagram. [a]These publications were included even if they did not meet all selection criteria (some publications were already included in the PubMed database search), and were generally cited within review articles identified in the literature search; [b]Included 17/34 key publications; [c]Key publications, no other reviews were included; [d]Excluded from initial search because title did not contain details on dosing regimen ($n = 2$) or the study was a 3-year RWD extension of an RCT already included in literature review ($n = 1$). [e]One study [41] did not specify asthma severity but was used for supplementary information for AHEAD [40] and COMPASS [43], two studies that used MART in moderate asthma. *FP* fluticasone propionate, *MART* maintenance and reliever therapy, *QD* once-daily, *RCT* randomized controlled trial, *RWD* real-world data

cortisol suppression ranging from 4.2% to 5.3%. The total 28-day ICS dose was 2600 µg, 2900 µg, and 3000 µg for SYGMA-1, SYGMA-2, and Novel START, respectively. The as-needed BUD dosing arm from a fourth clinical trial (PRACTICAL) [10] was also in the low airway efficacy/low systemic activity quadrant, with slightly higher bronchoprotection (45.8%) and cortisol suppression (8.5%) than the other clinical trials or irregular ICS dosing simulations, and a higher total 28-day ICS dose (4900 µg).

Both 50% adherence simulations fell in the low airway efficacy/low systemic activity quadrant, with FP 200 µg and BUD 200 µg daily dosing having similar degrees of bronchoprotection (52.3% and 51.3%, respectively) and cortisol suppression (8% and 9.5%, respectively). The total 28-day ICS dose was 5600 µg in FP and BUD 50% adherence simulations.

The 70% and 100% adherence simulations for FP 200 µg and BUD 200 µg regular daily dosing, and the regular daily BUD dosing arms from two clinical trials [10, 11] fell within the high airway efficacy/low systemic activity quadrant. SYGMA-1 and PRACTICAL had 80.6% and 77.1% bronchoprotection and 14.2% and 13.7% cortisol suppression, respectively, and the total 28-day ICS dose was 8800 µg and 8500 µg, respectively. Patients in the SYGMA-1 and PRACTICAL studies had higher adherence to treatment than patients in SYGMA-2 and Novel START, explaining why BUD 200 µg regular daily dosing in SYGMA-1 and PRACTICAL fell in the high airway efficacy/low systemic

Table 1 Summary of all articles from data extraction grouped by asthma severity and used for BUD and FP dose–response modeling

Study	Asthma severity	Study design	Patient age/age range, years	ICS treatment(s) and dosing regimen(s)	Primary endpoint
O'Byrne et al. 2018 (SYGMA-1) [11]	Mild	52-week double-blind trial	≥ 12	Placebo + BUD/FOR PRN BUD BID	Superiority of BUD PRN to TRB PRN measured by weeks with well-controlled asthma
Bateman et al. 2018 (SYGMA-2) [8]	Mild	52-week double-blind trial	≥ 12	Placebo + BUD/FOR PRN BUD BID	Non-inferiority of BUD/FOR PRN to BUD BID measured by annualized rate of severe exacerbations
Beasley et al. 2019 (Novel START) [9]	Mild	52-week open-label, parallel-group trial	18–75	BUD/FOR PRN BUD BID	Superiority of BUD/FOR PRN to albuterol PRN measured by annualized rate of asthma exacerbations
Hardy et al. 2019 [10]	Mild to moderate	52-week open-label, multi-center trial	18–75	BUD/FOR PRN BUD BID	Superiority of BUD/FOR PRN to BUD BID measured by number of severe asthma exacerbations per patient per year
Bousquet et al. 2007 (AHEAD) [40]	Moderate	26-week, randomized, double-blind, parallel-group, multinational study	≥ 12	BUD/FOR MART FP/SAL BID	Superiority of BUD/FOR MART vs. FP/SAL BID + TRB PRN. Primary variable, time to first severe exacerbation
Kuna et al. 2007 (COMPASS) [43]	Moderate	6-month, randomized, double-blind study	≥ 12	BUD/FOR MART BUD/FOR BID FP/SAL BID	Comparison of BUD/FOR MART with SAL/FP BID and BUD/FOR BID (both BID treatments with TRB for relief). Primary variable, time to first severe exacerbation
Lin et al. 2012 [34]	Moderate	6-month, multicenter, randomized, parallel-group, double-blind, active-drug-controlled study	≥ 12	BUD/FOR MART FP/SAL BID	Compare BUD/FOR MART and high-dose FP/SAL BID + TRB PRN. Primary variable, time to first severe exacerbation

Table 1 continued

Study	Asthma severity	Study design	Patient age/age range, years	ICS treatment(s) and dosing regimen(s)	Primary endpoint
Patel et al. 2013 [30]	Moderate	24-week, randomized, open-label, parallel-group trial	16–65	BUD/FOR MART BUD/FOR BID	Proportion of participants with ≥ 1 episode of high use of β-agonist (> 8 actuations per day of BUD/FOR in addition to 4 maintenance doses in the MART group, or > 16 actuations per day of SAL in the standard group) during the study
Pavord et al. 2009 [29]	Moderate	1-year, double-blind, randomized, parallel-group study	18–65	BUD/FOR MART BUD/FOR BID	Comparison of the effects of BUD/FOR MART with BUD/FOR BID. Two primary variables: change in induced sputum eos count from baseline, and change in number of eos/mm^2 of subepithelial tissue in bronchial biopsies from baseline to week 52
Ställberg et al. 2015 [25]	Moderate	1-year observational study	17–89	BUD/FOR MART	Examination of maintenance and as-needed BUD/FOR use. Primary variable, total number of BUD/FOR inhalations/day
Vogelmeier et al. 2005 (COSMOS) [21]	Moderate	1 year, randomized, open-label, parallel-group study	≥ 12	BUD/FOR MART FP/SAL BID	Comparison of effectiveness of BUD/FOR BID + PRN vs. control group (FP/SAL + ALB). Primary variable, time to first severe exacerbation

ALB albuterol, *BID* twice daily, *BUD* budesonide, *eos* eosinophil, *FOR* formoterol, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *MART* maintenance and reliever therapy, *PRN* as needed, *RCT* randomized controlled trial, *SAL* salmeterol, *TRB* terbutaline

Table 2 Summary of daily BUD and FP doses in mild asthma studies

Study	Treatment arm	Total daily ICS dose, µg	Median daily ICS dose, µg	Mean daily ICS dose, µg	Median MED, µg/day	Median days' use of ICS
O'Byrne et al. 2018 (SYGMA-1) [11]	Placebo + BUD/FOR 200/6 µg PRN	NE	57	93	NE	NE
	BUD 200 µg BID + TRB PRN	400	340	315	NE	NE
Bateman et al. 2018 (SYGMA-2) [8]	Placebo + BUD/FOR 200/6 µg PRN	NE	66	104	NE	30.5
	BUD 200 µg BID + TRB PRN	400	267	251	NE	67.9
Beasley et al. 2019 (Novel START) [9]	BUD/FOR 200/6 µg PRN	NE	NE	107 (109)[a]	NE	NE
	BUD 200 µg BID + SAL 100 µg PRN	400	NE	222 (113)	NE	NE
Hardy et al. 2019 [10]	BUD 200 µg BID + TRB 250 µg PRN	400	NE	302 (84.8)[a]	NE	NE
	BUD/FOR 200/6 µg PRN	NE	NE	176 (143)	NE	NE

BID twice daily, *BUD* budesonide, *FOR* formoterol, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *MED* minimum effective dose, *NE* not evaluated, *PRN* as needed, *SAL* salmeterol, *SD* standard deviation, *TRB* terbutaline
[a]Mean (SD)

activity quadrant while SYGMA-2 and Novel START were in the low airway efficacy/low systemic activity quadrant. The 100% adherence simulations offered maximum bronchoprotection for FP 200 µg (99.9%) and BUD 200 µg (100.0%), with cortisol suppression being lower with FP 200 µg (14.8%) than BUD 200 µg (17.4%). The FP 200 µg 70% adherence simulation had similar bronchoprotection and cortisol suppression (73.6% and 10.9%, respectively) to the BUD 200 µg adherence simulation (71.7% and 12.9%, respectively). Total 28-day ICS dose was 11,200 µg in FP and BUD 100% adherence simulations, and 7840 µg in FP and BUD 70% adherence simulations.

ICS Airway Efficacy and Systemic Activity in Moderate-to-Severe Asthma

The mean daily ICS dose data that were extracted from available data in studies used for the moderate-to-severe asthma simulations are detailed in Table 3.

In both the moderate (Fig. 4A) and moderate-to-severe asthma (Fig. 4B) scenarios, most studies with MART dosing [21, 25, 29, 30, 34, 40, 43] and most adherence simulations (BUD 400 µg and 800 µg, FP 500 µg) fell within the high airway efficacy/high systemic activity quadrant. All final data from the

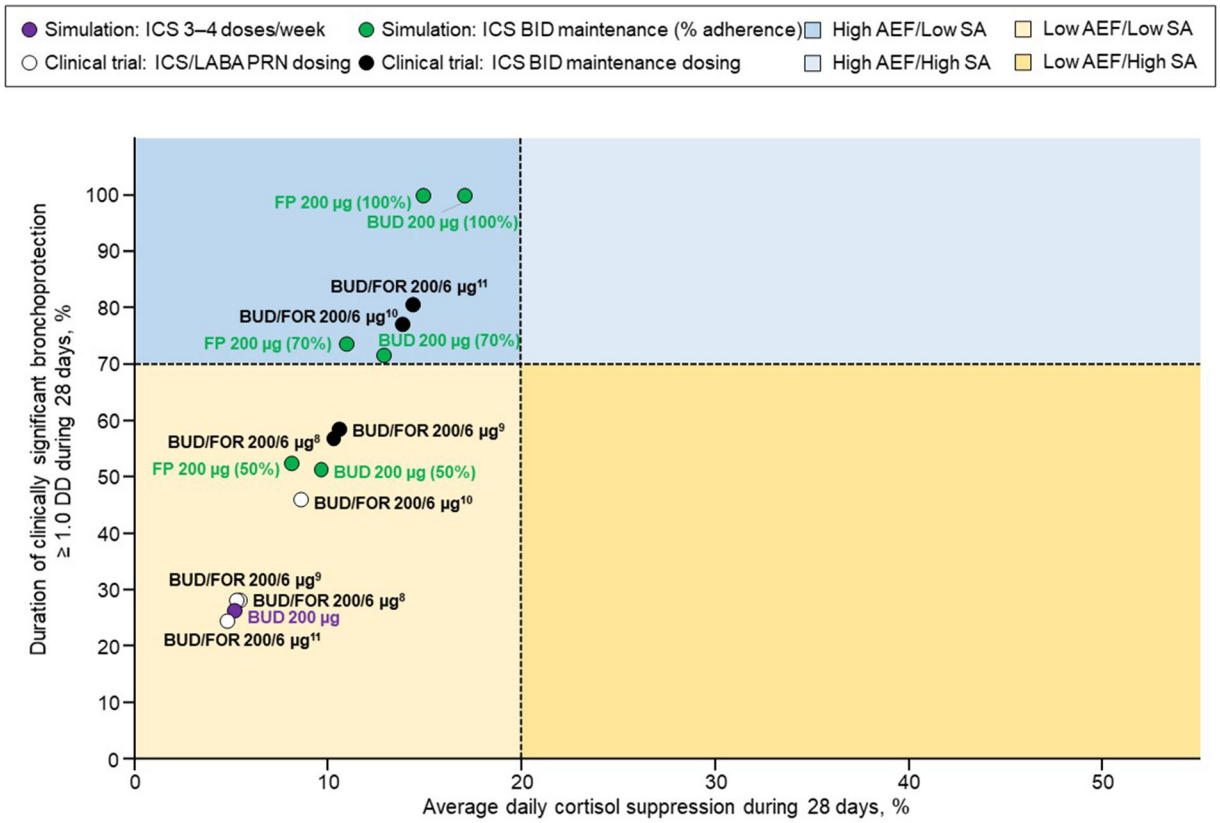

Fig. 3 Comparison of airway efficacy to systemic activity for BUD/FOR as-needed and regular ICS dosing regimens in mild asthma [8–11]. *AEF* airway efficacy, *BID* twice daily, *BUD* budesonide, *DD* doubling dose, *FOR* formoterol, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *PRN* as needed, *SA* systemic activity

moderate and moderate-to-severe asthma simulations are provided in Supplementary Table S3.

In the moderate asthma simulations, a ≥ 1.5 doubling dose efficacy threshold was used (Fig. 4A), simulations of 100% adherence with BUD/FOR 800 µg, BUD/FOR 400 µg, and FP/SAL 500 µg offered maximum bronchoprotection (100.0%), falling within the high efficacy/high systemic activity quadrant; BUD/FOR 800 µg had the highest cortisol suppression (45.7%) followed by FP/SAL 500 µg (30.3%) and BUD/FOR 400 µg (29.7%). Simulations of 85% adherence with these three treatments were also in the high efficacy/high systemic activity quadrant, with 87.0–92.1% bronchoprotection and 26.4–41.7% cortisol suppression across simulations. For BUD/FOR 800 µg, BUD/FOR 400 µg, and FP/SAL 500 µg, total 28-day ICS doses were 44,800 µg, 22,400 µg, and 28,000 µg, respectively, for 100% adherence simulations, and 38,080 µg, 19,040 µg, and 23,800 µg, respectively, for 85% adherence simulations. Total 28-day ICS doses were the same in both the moderate and moderate-to-severe asthma simulations.

In the moderate-to-severe asthma simulations where a ≥ 2.0 doubling dose efficacy threshold was used (Fig. 4B), all adherence simulations showed greater variation in the proportions of bronchoprotection (ranging 71.4–100.0%) and cortisol suppression (ranging 26.4–45.7%) when compared with the moderate asthma simulations with a 1.5 doubling dose efficacy threshold, but all remained in the high efficacy/high systemic activity quadrant. Five of the clinical trials with a BUD/FOR MART 200/6 µg (two inhalations BID plus as-needed

Table 3 Summary of mean daily BUD and FP doses in moderate asthma studies

Study	Treatment arm[a]	Mean daily ICS dose, µg/day
Bousquet et al. 2007 (AHEAD) [40]	BUD/FOR 200/6 µg MART	990
	FP/SAL 500/50 µg BID + TRB PRN	1000
Kuna et al. 2007	FP/SAL 125/25 µg BID + TRB PRN	500
(COMPASS) [43]	BUD/FOR 320/9 µg BID + TRB PRN	640
	BUD/FOR 200/6 µg MART	650
Lin et al. 2012 [34]	BUD/FOR 200/6 µg MART	978
	FP/SAL 500/50 µg + TRB PRN	1000
Patel et al. 2013 [30]	BUD/FOR 200/6 µg MART	943.3 (1502.5)[b]
	BUD/FOR 200/6 µg BID + ALB PRN	684.3 (390.5)[b]
Pavord et al. 2009 [29]	BUD/FOR 200/6 µg MART	604
	BUD/FOR 800/12 µg BID + TRB PRN	1600
Ställberg et al. 2015 [25]	BUD/FOR 80/4.5 µg MART	268
	One inhalation	
	BUD/FOR 200/6 µg MART	546
	One inhalation	
	BUD/FOR 200/6 µg MART	1016
	Two inhalations	
Vogelmeier et al. 2005	BUD/FOR 200/6 µg MART	918
(COSMOS) [21]	FP/SAL 250/50 µg + ALB PRN	583

ALB albuterol, *BID* twice daily, *BUD* budesonide, *FOR* formoterol, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *MART* maintenance and reliever therapy, *PRN* as needed, *SAL* salmeterol, *SD* standard deviation, *TRB* terbutaline
[a]Only BID dosing, ICS-containing treatment arms shown
[b]Mean (SD)

inhalations) treatment arm [21, 25, 30, 34, 40] fell in the high efficacy/high systemic activity quadrant in both the moderate asthma and moderate-to-severe asthma simulations. Bronchoprotection ranged from 91.1% to 92.4% and from 79.9% to 83.4% in the moderate and moderate-to-severe asthma simulations, respectively; cortisol suppression was similar in both models and ranged from 32.6% to 34.9%. Total 28-day ICS doses across these clinical trials was also similar, ranging from 25,648 µg to 28,448 µg.

Notably, when changing from a ≥ 1.5 doubling dose threshold in the moderate asthma simulations to a ≥ 2.0 doubling dose threshold in the moderate-to-severe asthma simulations, the 85% and 100% adherence simulations for FP/SAL 250 µg BID dosing moved from the high airway efficacy/low systemic activity quadrant to the low airway efficacy/low systemic activity quadrant. Bronchoprotection fell from 90.4% and 73.8% to 32.5% and 23.6% for 100% and 85% adherence, respectively (average daily cortisol suppression did not change for either simulation). This was consistent with high ICS

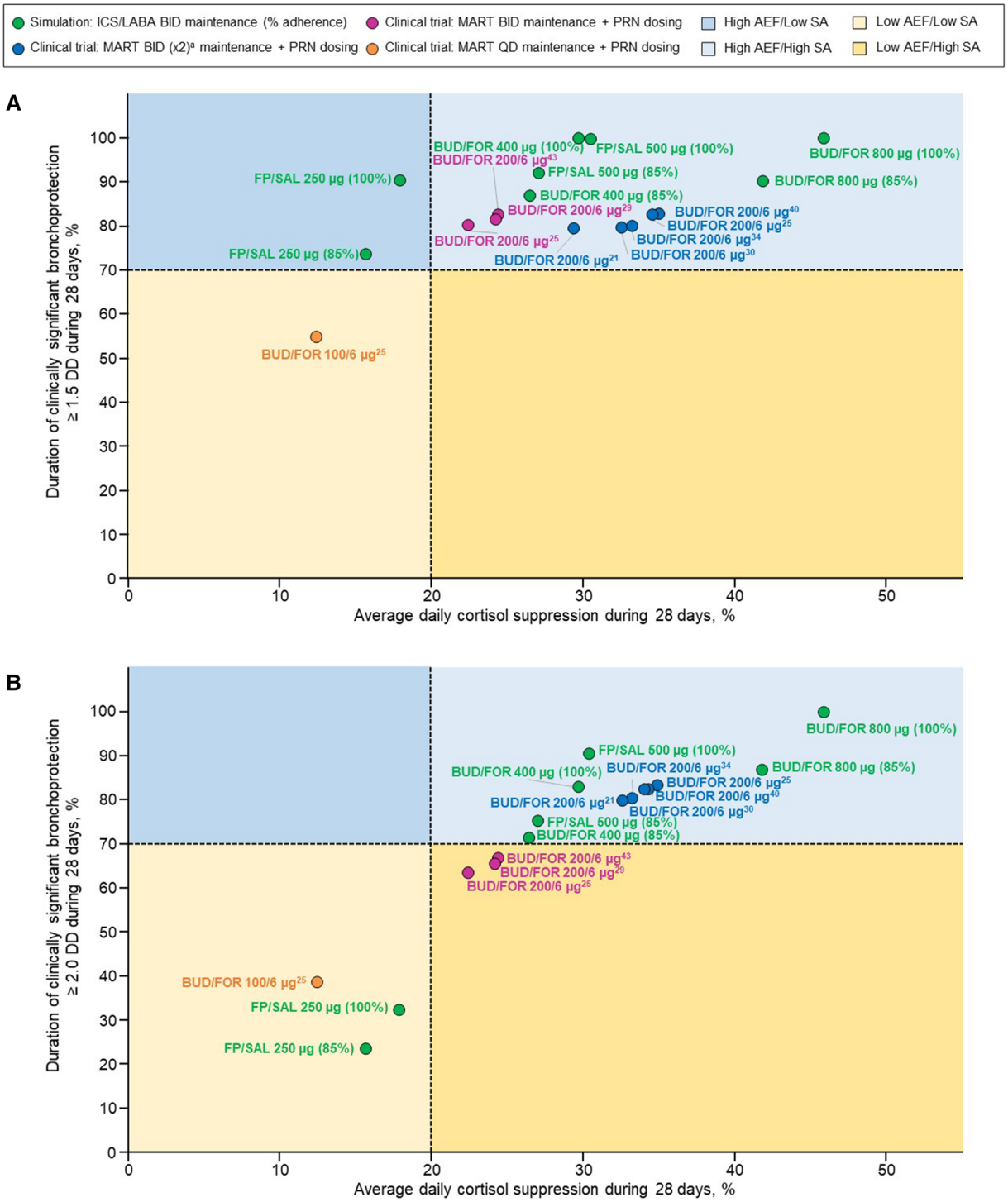

Fig. 4 Comparison of airway efficacy to systemic activity for BUD/FOR MART and regular ICS/LABA dosing regimens in (**A**) moderate asthma and (**B**) moderate-to-severe asthma [21, 25, 29, 30, 34, 40, 43]. [a]Two inhalations BID. *AEF* airway efficacy, *BID* twice daily, *BUD* budesonide, *DD* doubling dose, *FOR* formoterol, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *LABA* long-acting bronchodilator, *MART* maintenance and reliever therapy, *QD* once daily, *PRN* as needed, *SA* systemic activity, *SAL* salmeterol

doses being needed for more severe asthma [1] and demonstrated that FP 250 μg did not meet the efficacy threshold for severe asthma. Additionally, three of the clinical trials with a BUD/FOR MART 200/6 μg (one inhalation BID plus as-needed inhalations) treatment arm [25, 29, 43] moved from the high airway efficacy/high systemic activity quadrant to the low airway efficacy/high systemic activity quadrant, with bronchoprotection dropping from approximately 80.0% to approximately 65.0% across studies (cortisol suppression did not change). Total 28-day ICS dose ranged from 15,288 μg to 17,080 μg across studies.

BUD/FOR MART 100/6 μg (one inhalation/day plus as-needed inhalations) fell in the low airway efficacy/low systemic activity quadrant in both the moderate asthma and moderate-to-severe asthma simulations. Bronchoprotection was higher in the moderate asthma simulations (55.0%) than the moderate-to-severe asthma simulations (38.6%); cortisol suppression in both models was 12.4%, and total 28-day ICS dose was 7504 μg.

DISCUSSION

The data extracted from our structured literature review were used to explore the relationship between ICS dosing regimen and risk–benefit profile (in terms of bronchoprotection and cortisol suppression). Additionally, we explored how adherence could potentially affect the risk–benefit profile in patients with mild, moderate, and moderate-to-severe asthma. With a specific focus on BUD or FP-containing treatments, we found that regular daily ICS and ICS/LABA dosing had more bronchoprotection than as-needed BUD/FOR dosing or BUD/FOR MART dosing, and still maintained low systemic activity. We also found that the benefits of regular daily ICS dosing regimens were diminished with low (50%) adherence, resulting in a shorter duration of bronchoprotection more like typical as-needed BUD/FOR usage. These findings have implications for clinicians choosing treatment options for asthma management, and for the advice they give their patients.

To adequately control underlying airway inflammation and, subsequently, reduce symptoms and exacerbations in patients with asthma, it is important that ICS or ICS-containing dosing regimens are appropriately prescribed and that patients adhere to their prescribed treatment. Our mild asthma simulations indicated that regular daily BUD and FP dosing had an ICS benefit–risk profile in the optimum range (high efficacy/low systemic activity) for asthma control, and that the benefit–risk profile of an as-needed or irregular dosing regimen (plus regimens with 50% adherence) fell within the suboptimum range (low efficacy/low systemic activity) for BUD and FP. These dose regimens are expected to have compromised airway anti-inflammatory activity, which may lead to inadequate asthma control. Clinical trial findings show that irregular, as-needed BUD/FOR dosing provides less overall symptom relief and fewer quality-of-life improvements than regular daily ICS dosing [9, 11], but provides some benefit in exacerbation reduction or, at least, is non-inferior to daily dosing in this regard [8–10], which is mostly consistent with our analysis. Our literature search identified no unexpected safety findings: various doses of BUD, FP, BUD/FOR, and FP/SAL were well tolerated across studies. Higher ICS doses (albeit still in the recommended dose range) may better control underlying airway inflammation [22] and provide greater therapeutic benefits than lower doses [48]. This was generally consistent with our simulations, wherein higher total 28-day doses of ICS conferred higher bronchoprotection than lower doses and near maximal (100%) bronchoprotection was achievable with high adherence. However, consistent with literature describing the negative effects of poor treatment adherence on efficacy [3, 4], our mild asthma simulations found that lower (50%) adherence to daily doses of BUD and FP fell within the low airway efficacy/low systemic activity quadrant, whereas 70% and 100% adherence to BUD and FP moved bronchoprotection into the optimal ICS benefit–risk quadrant (high airway efficacy/low systemic activity). Existing reviews and studies have reported varying degrees of treatment

adherence in patients with asthma [58–60], several of which report adherence below the magnitude simulated in our analysis; thus, in practice, patients with lower adherence would likely not have levels of bronchoprotection as high as those in our model, but our findings nevertheless suggest improved patient education on the importance of treatment adherence would benefit patients with asthma. Our moderate and moderate-to-severe asthma analyses also found that regular daily dosing with ICS/LABA (at adherence $\geq$ 85%) offered the highest levels of bronchoprotection compared with BUD/FOR MART dosing. Regular daily FP/SAL dosing with 85% and 100% adherence in moderate asthma offered the optimal ICS benefit/risk ratio.

Mixed results regarding the benefits of regular daily ICS/LABA dosing over MART dosing have been reported in the literature. For instance, studies have reported benefits of BUD/FOR MART dosing over FP/SAL daily dosing (plus an as-needed SABA), including a reduction in exacerbation rate [21, 34] and improvements to lung function [21, 34, 37], and have also found that both of these treatment approaches had similar benefits in improving lung function, asthma control, and quality of life [40, 43]. Studies of BUD/FOR MART versus daily BUD/FOR dosing (plus an as-needed SABA) also had mixed results. We identified studies wherein MART was associated with fewer severe exacerbations [30] and similar asthma control [29] compared with daily BUD/FOR regular dosing, and was associated with a high proportion of rescue-medication-free days [25]. Variations in the daily ICS dose were also reported: BUD/FOR MART had a lower ICS exposure compared with daily dosing with FP/SAL or BUD/FOR in some studies [34, 37, 40, 43], but a similar exposure to FP/SAL daily dosing in another [21]. The inconsistent effects of MART and variation in average daily ICS dose likely reflect MART use in a real-life setting, where the actual ICS dose per day will vary greatly from patient to patient depending on how many as-needed inhalations are required for symptom control and, furthermore, whether patients are using their MART dosing regimen as prescribed. For instance, patients prescribed MART may only use their inhaler for maintenance therapy and use a different SABA for relief, or do not collect enough prescription fills to use the same inhaler for maintenance and relief [61, 62]. In these cases, the delivered dose of ICS will likely not be enough to confer adequate bronchoprotection and, as such, long-term symptom control will be poor. There is a view that taking an as-needed dose of ICS with a bronchodilator to control symptoms is better than taking no ICS at all, but this hypothesis is unsupported by literature. Indeed, as demonstrated from the literature and our analysis, regular dosing provides superior asthma control and bronchoprotection over irregular or as-needed ICS/ICS-containing dosing regimens. An additional point to consider in the various outcomes of MART versus ICS/LABA regular dosing is that, while MART is effectively an asthma action plan, most studies did not include a written action plan for the regular dosing arm, which has been shown to consistently improve asthma health outcomes [63]. Our analyses in moderate and moderate-to-severe asthma were consistent with the available literature and showed a range of airway efficacies and systemic activities between different MART approaches, with several dosing regimens having a high ($>$ 70%) degree of bronchoprotection, but none of the MART approaches fell within the high airway efficacy/low systemic activity quadrant. Thus, inappropriate BUD/FOR MART use and prescribing have implications for both patient and physician education on the pharmacological implications of MART with a short-acting ICS (such as BUD), and on how regular daily dosing with ICS/LABA is required to maintain control of underlying airway inflammation and breakthrough symptoms.

A potential limitation of this study was that in modeling the bronchoprotective effects of each ICS or ICS/LABA, we only estimated the effect of the ICS arising from its anti-inflammatory mechanism of action. SABAs and LABAs do not possess anti-inflammatory activity but can have a bronchoprotective effect that can be assessed via direct challenge agents that act on smooth muscle (such as methacholine). However, as the effect of SABAs and LABAs on bronchoprotection assessed via AMP challenge

is likely to be minor and short-lived, the major contribution from ICS/LABAs to bronchoprotection will be from the ICS component [64]. Additionally, our study did not consider the effects of ICS dosing regimens on airway remodeling, which is a point of interest in asthma management [65], and did not consider any potential sex-specific differences in treatment response or adherence modeling outputs—two areas that could be worth exploring in future studies. A further limitation was that we only included widely available and twice-daily ICS and ICS-containing regimens in our analysis. The safety of LABAs like FOR used in mild asthma on an as-needed basis with BUD, or in a MART dosing regimen in moderate asthma, needs to be studied further.

To summarize, flexible dosing regimens (BUD/FOR as-needed or MART dosing) may not be the optimal pharmacological approach to manage all patients with asthma in clinical practice. Regular proactive dosing with ICS or ICS/LABA is more likely to deliver the optimal ICS amount within the benefit/risk range to adequately treat the underlying inflammation. This analysis included a wide spectrum of asthma severity that may translate into clinical practice and change therapeutic approach.

CONCLUSIONS

Regular daily ICS or ICS/LABA dosing regimens with BUD or FP had higher airway efficacy but with similarly low systemic activity compared with as-needed BUD/FOR dosing in mild asthma, and MART in moderate and moderate-to-severe asthma, respectively. Regular daily ICS/LABA had a better benefit–risk profile than BUD/FOR MART in moderate-to-severe asthma. Overall, the daily ICS dose and treatment adherence also impacted upon airway efficacy and systemic activity in mild, moderate, and moderate-to-severe asthma models. Higher ICS doses and higher adherence generally provided the best bronchoprotection in mild, moderate, and moderate-to-severe asthma.

Regular daily ICS or ICS/LABA dosing regimens with BUD or FP had higher airway efficacy with similarly low systemic activity compared with as-needed BUD/FOR dosing in mild asthma, and MART in moderate and moderate-to-severe asthma, respectively.

Further study of different dosing regimens in asthma in real-world settings would be beneficial in guiding clinical practice and helping to optimize patient care.

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Data Availability. Data sharing not applicable to this article as no datasets were generated or analyzed during the current study. Trademarks are owned by or licensed to their respective owners (SYMBICORT [AstraZeneca]).

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