



Benefit:Risk Profile of Budesonide in Obstructive Airways Disease

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Abstract

Airway inflammation is a major contributing factor in both asthma and chronic obstructive pulmonary disease (COPD) and represents an important target for treatment. Inhaled corticosteroids (ICS) as monotherapy or in combination therapy with long-acting β_2 -agonists or long-acting muscarinic antagonists are used extensively in the treatment of asthma and COPD. The development of ICS for their anti-inflammatory properties progressed through efforts to increase topical potency and minimise systemic potency and through advances in inhaled delivery technology. Budesonide is a potent, non-halogenated ICS that was developed in the early 1970s and is now one of the most widely used lung medicines worldwide. Inhaled budesonide's physiochemical and pharmacokinetic/pharmacodynamic properties allow it to reach a rapid and high airway efficacy due to its more balanced relationship between water solubility and lipophilicity. When absorbed from the airways and lung tissue, its moderate lipophilicity shortens systemic exposure, and its unique property of intracellular esterification acts like a sustained release mechanism within airway tissues, contributing to its airway selectivity and a low risk of adverse events. There is a large volume of clinical evidence supporting the efficacy and safety of budesonide, both alone and in combination with the fast- and long-acting β_2 -agonist formoterol, as maintenance therapy in patients with asthma and with COPD. The combination of budesonide/formoterol can also be used as an as-needed reliever with anti-inflammatory properties, with or without regular maintenance for asthma, a novel approach that is already approved by some country-specific regulatory authorities and currently recommended in the Global Initiative for Asthma (GINA) guidelines. Budesonide remains one of the most well-established and versatile of the inhaled anti-inflammatory drugs. This narrative review provides a clinical reappraisal of the benefit:risk profile of budesonide in the management of asthma and COPD.

1 Introduction

Chronic airway inflammation is a characteristic feature of asthma and chronic obstructive pulmonary disease (COPD), and is therefore an important target for treatment [1, 2]. Use of glucocorticosteroids (corticosteroids) has been investigated in both conditions [3–7], with the first successful treatment of asthma with an oral corticosteroid (OCS) reported in 1950 [3, 8]. However, although highly effective, long-term use of OCS was soon found to be associated with serious

adverse effects, including osteoporosis, diabetes, Cushing's syndrome, acne, skin thinning and bruising [8].

Following early trials of inhalation with various dermal hydrocortisone formulations [9, 10], second- and third-generation dermal steroids were developed by medicinal chemists who focused on increasing potency through addition of the halogens chlorine or fluorine [11], leading to the first successful inhaled corticosteroid for the treatment of asthma in 1972: beclomet(h)asone dipropionate (BDP) [5]. However, BDP was selected on the basis of its high topical efficacy on the skin and was not specifically optimised to reduce its systemic risks when absorbed via other routes. In contrast, given the known systemic side effect liability of second- and third-generation halogenated steroids, budesonide (developed in the same period as the BDP inhalation findings) was screened primarily for improved topical selectivity [12, 13]. Budesonide was found to have a better topical selectivity than that of BDP, flucinolone acetonide, flunisolide (FLU) and triamcinolone acetonide (TA) [12, 13]. Thus, budesonide was the first topical corticosteroid selected for improved local selectivity, and its rapid uptake into tissue made it a good prospect for inhalation therapy. This was the

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Key Points

Inhaled corticosteroids are the cornerstone of current treatment for asthma and are also widely used in combination with a long-acting β_2 -agonist with or without a long-acting muscarinic antagonist in the management of patients with moderate-to-severe chronic obstructive pulmonary disease.

Budesonide is a long-established inhaled corticosteroid and its unique molecular structure and pharmacokinetic/pharmacodynamic properties underpin its rapid efficacy and favourable safety profile.

Budesonide may be used as maintenance therapy in patients with moderate-to-severe asthma and is recommended in global asthma management guidelines for use in combination with the bronchodilator formoterol as an as-needed reliever with anti-inflammatory properties, with or without regular maintenance therapy.

basis for its development for asthma and eventual use in the treatment of COPD.

This clinical utility has given further impetus to the development of newer inhaled corticosteroids (ICS), and FLU, fluticasone propionate (FP), ciclesonide (CIC), mometasone furoate (MF), and fluticasone furoate (FF) have been approved since the introduction of beclometasone and budesonide. These newer compounds were designed primarily for enhanced lipophilicity, which prolonged intraluminal airway retention time with the aim of achieving efficacy with once-daily dosing. However, this approach also introduced potential issues around longer localised airway immunosuppression, potentially enhancing the risk of pneumonia and other respiratory infections [14]. The raised lipophilicity also prolongs the terminal half-life in the systemic circulation, which increases the risk of systemic adverse effects [15–17].

Today, ICS are recommended in guidelines as the cornerstone of pharmacotherapy for patients with persistent asthma across all severities, and also in combination with a long-acting β_2 -agonist (LABA) for patients with moderate to severe asthma [18]. ICS are considered by the Global Asthma Network guidance as the first-line asthma preventer for patients with persistent or frequent symptoms, and in combination with LABA (ICS/LABA) are envisaged to have an ever-increasing role in the treatment of asthma [19]. Indeed, two ICS and one ICS/LABA combination are listed on the World Health Organization's Model List of Essential Medicines [19]. Furthermore, they remain the only class of anti-asthma drug proven to reduce asthma deaths [20]. In COPD, ICS are recommended in combination with LABA by current guidelines for patients with moderate-to-very

severe COPD at high risk of exacerbations, since this combination improves both symptoms and lung function and reduces exacerbation risk [21].

In this narrative review, based on the authors' collective expertise, we provide a clinical reappraisal of the benefit:risk profile of budesonide in the management of asthma and COPD, after a brief overview of the pharmacodynamics of ICS.

2 Brief Overview of Inhaled Corticosteroids (ICS) Pharmacodynamics

2.1 Mechanisms of Action of ICS in Asthma and Chronic Obstructive Pulmonary Disease (COPD)

ICS diffuse through cell membranes and subsequently bind to the glucocorticoid receptor (GCR). The GCR, which is believed to share a common ancestral receptor type with the mineralocorticoid and progesterone receptors (MR and PR), is present in the cytoplasm of most human cell types, bound to HSP90 chaperone proteins [22–24]. Binding results in dissociation of HSP90 and formation of an activated GCR–corticosteroid complex. Subsequent translocation across the nuclear membrane, interaction with other nuclear transcription factors, and homodimeric binding to specific deoxyribonucleic acid (DNA) sequences allow the regulation of gene transcription and protein synthesis [22, 23]. In the airways and lungs, corticosteroids interact with the GCR following inhalation and absorption into airway mucosa and the tissues below.

Whereas most drugs have a narrow 'therapeutic window', corticosteroids can exert their effects over a broad concentration range [25]. This is due to the existence of multiple mechanisms of action. Broadly, the steroid-activated GCR can be viewed as a ligand-regulated transcription factor, which controls a very diverse set of genes. Most actions of corticosteroids are mediated by the pleiotropic effects of GCRs on multiple signalling pathways [23, 26, 27]. Three major classes of action relevant for control of asthma and COPD have been described: (1) directly regulating the expression of inflammatory genes encoding cytokines, chemokines, adhesion molecules, inflammatory enzymes, receptors and proteins by binding to positive or negative glucocorticoid response elements (GRE); (2) binding to and sequestering other transcription factors, such as nuclear factor (NF)- κ B; and (3) directing DNA three-dimensional histone protein binding architectures via the counterbalanced activity of histone acetyltransferases and histone deacetylases, thus regulating access to the transcriptional gene machinery [28].

Microarray analyses of cultured airway epithelial cells have enabled detailed mapping of genes affected by budesonide treatment [29]. A single, high-dose budesonide inhalation led to a ≥ 2 -fold increase in the expression of 46 genes in bronchial biopsy samples within 6 h [30]. Upregulated genes included those inhibiting NF- κ B and AP-1, the dual-specificity phosphatase-1 that controls activated mitogen-activated protein kinases (MAPK), and inhibitors of G-protein coupled receptors and T-cell chemotaxis. There were also 10 downregulated genes whose expression decreased by at least 50% following budesonide inhalation, including genes for chemokines, metalloproteases and Toll-like receptors.

Another potential mechanism of action of ICS involves protection against oxidative or viral damage to the epithelial barrier function. In cultured human epithelial cell lines, budesonide protected barrier function significantly more effectively than FP in response to cigarette smoke extract, possibly due to attenuation of epidermal growth factor receptor-dependent glycogen synthase kinase-3 β phosphorylation [31].

However, there are also some faster, non-genomic mechanisms that inhibit the production of mediators associated with inflammatory cells in the airways [22, 26], such as GCR-dependent inhibition of the MAPK pathway [32, 33]. Rapid change in airway blood flow is a non-genomic parameter that reflects bronchial vascular response to ICS. Corticosteroids inhibit organic cation transporters (OCT), such as OCT-3, expressed by the vascular smooth muscle cells, resulting in an increase of adrenergic agonists at α -adrenergic receptor sites [34]. ICS can therefore reduce the airway hyperaemia that is both a manifestation of inflammation and a contributory factor to further inflammation. Budesonide has been shown to rapidly reduce airway hyperaemia, and was significantly more potent in this respect than BDP, and more potent than FP in asthmatic subjects in one comparative study [35].

2.2 Corticosteroid Chemical Structure–Activity Relationship

All corticosteroids consist of a hydrogenated cyclopentanoperhydrophenanthrene ring system, with three cyclohexane rings and one cyclopentane ring [36] and a range of different substituents. It is the nature and position of these substitutions that determine differences in their potency and clinical efficacy (Fig. 1) [37]. Key positions that affect potency are halogenation of the 6 and 9 positions [38], while R-substitution at the 16 α and 17 α positions affects lipophilicity. Also, R-substitution at the 17 position affects the glucocorticoid potency. Budesonide is a non-halogenated ICS that has lipophilic substitutions at the 16 α and 17 α positions and a hydroxyl group at the C21 position (Fig. 1) [13, 38].

Pharmacological and metabolic studies have shown that the non-symmetrical acetal substitution in the 16 α and 17 α positions optimises the ratio of topical to systemic activity [12, 38, 39]. After systemic uptake, budesonide's non-symmetrical acetal group can be split by liver enzymes, resulting in metabolites with much lower receptor affinity, which does not occur to the same extent for the symmetrical acetals of the 16 α ,17 α -acetonide glucocorticoids (e.g. FLU, TA) [40]. This, together with further biotransformation routes, improves the systemic tolerability of budesonide and enables dose escalation when required [41, 42].

2.3 Factors Affecting Lung Deposition

The clinical benefits of an inhaled therapy depend on drug particles being deposited in the airways/lungs, rather than swallowed or exhaled. Particles between 1–5 μ m in diameter are the optimal size for deposition in the central and peripheral airways [45, 46]. If particles < 1 μ m are not exhaled again [45], they may be deposited in the alveoli and rapidly absorbed into the systemic circulation [47, 48] while larger particles tend to impact on the oropharynx rather than reaching the central or peripheral airways/lung [46]. Along with particle size, lung deposition also depends on factors such as the velocity at which the particles are delivered and, with the dry powder inhaler (DPI), the peak inspiratory flow rate and internal resistance of the device [46].

3 Development of Budesonide

In the 1960s, researchers at the Swedish pharmaceutical company Bofors Nobel-Pharma (a project later incorporated into Astra AB) designed a novel series of potent non-symmetrical 16 α , 17 α -acetal corticosteroids [12, 13]. Using new functional screening models for local selectivity, including human forearm skin blanching potency tests, the lead compound, budesonide, was found to have a topical selectivity several-fold better than BDP and other dermal steroids. The first patent application was filed in 1972 and budesonide was selected as a candidate drug by Astra AB in 1974, with asthma as the primary indication. Positive initial study results led to the approval of budesonide in 1981 for daily maintenance treatment for asthma (Fig. 2) [49].

In the first studies in asthma, budesonide was delivered via a pressurised metered-dose inhaler (pMDI) [6, 50–55]. Dose-dependent improvements in peak expiratory flow (PEF) were demonstrated for daily doses of 400–1600 μ g [6] and, during the 1990s, the results from studies with budesonide in asthma supported early intervention with ICS after initial onset of symptoms [56–58]. This was shown to improve asthma control and potentially to prevent progression to chronic irreversible airway obstruction [59, 60].

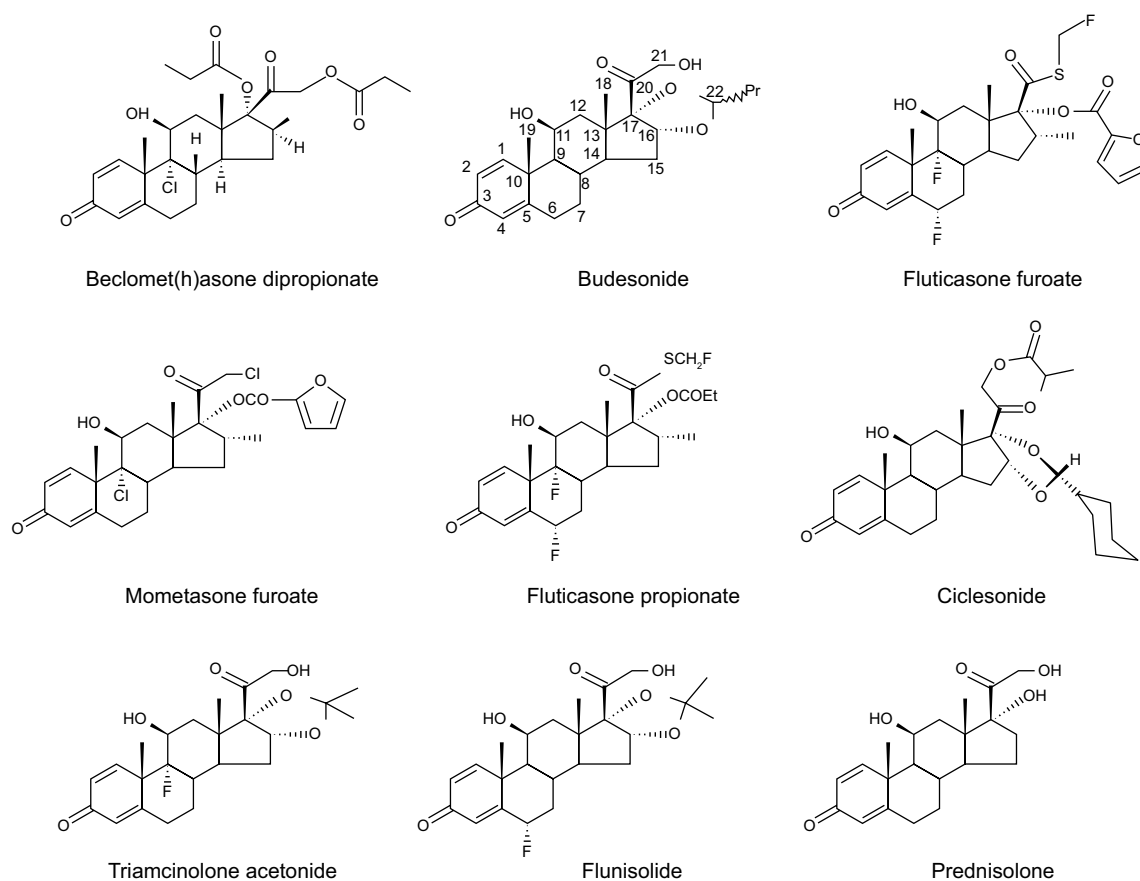


Fig. 1 The structures of inhaled corticosteroids [25]. Most ICS are administered as active compounds; however, beclometasone dipropionate and ciclesonide are prodrugs that require conversion to the active state by on-site hydrolysis in airway/lung tissue. This is due to

the fact they have a pre-existing ester at position C21. Ciclesonide is activated to desisobutryl-ciclesonide (des-CIC), and beclometasone dipropionate to beclometasone-17-monopropionate (BMP) [43, 44]. Adapted with permission from Daley-Yates [25]

These studies contributed to increased early use of ICS in asthma of all severities [58], and along with studies showing only small, transient effects on long-term growth in children [59, 61], were important factors in the recommendation of ICS as first-line therapy in asthma guidelines [37].

Also in the 1990s, advances in inhaler technology enabled greater efficiency of drug delivery. A comparison between the original suspension pMDI and the newly developed budesonide DPI, the Turbuhaler[®], found that lung deposition was approximately doubled with the DPI, with less variability, and only 50% higher systemic availability than with the pMDI [62]. This allowed the same degree of asthma control to be achieved with a lower dose, and with a reduced risk of systemic adverse effects, thus making twice-daily dosing feasible. Dose-dependent improvements in lung function were observed in two 12-week, randomised, placebo-controlled studies of budesonide Turbuhaler[®] in adults [63] or children [64] with moderate-to-severe persistent asthma. Budesonide twice daily via Turbuhaler[®] was significantly more effective than placebo, even at low doses (200 µg total

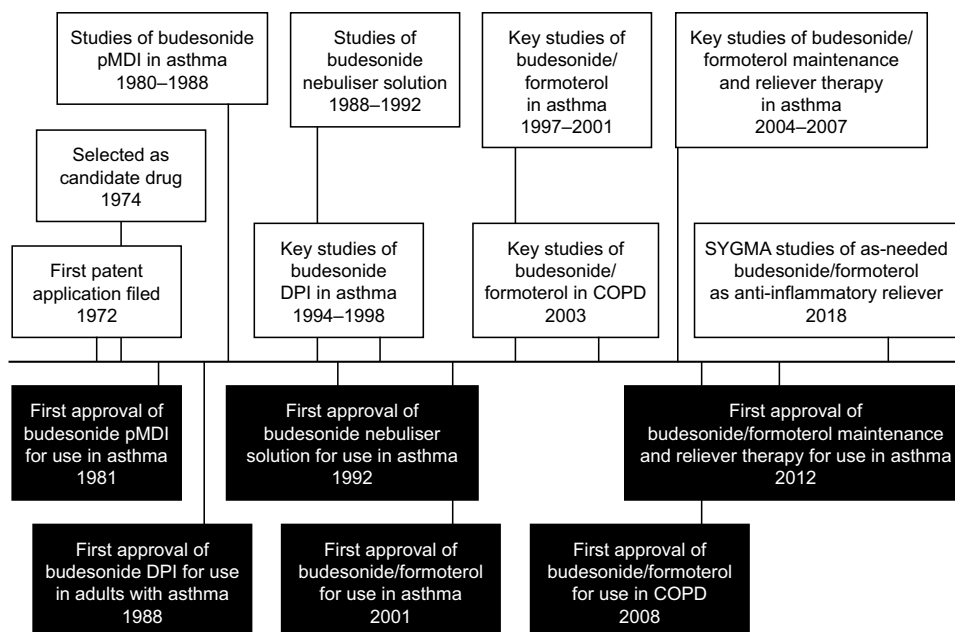
daily dose), and was well tolerated in both studies. A nebuliser suspension (Respules[®]) was subsequently developed for the treatment of very young children or other patients who were unable to use a handheld inhaler effectively [65].

Budesonide is currently available as a single-drug formulation in the Flexhaler[®] (in the US) or Turbuhaler[®] DPI (outside of the US), in the Respules[®] nebuliser suspension [65], and in combination with formoterol as a pMDI or DPI. Budesonide drug particles delivered via any of these technologies are within the optimal range of 1–5 µm [46]. Generic formulations are now available in some countries.

4 Properties of Budesonide

The development of ICS subsequent to budesonide aimed to improve once-daily efficacy by enhancing their lipophilicity [66], which is postulated to prolong their intraluminal airway deposition [25] and dissolution time [22]. However, the advantage gained by longer airway immunosuppression

Fig. 2 Key milestones in the development of budesonide. *COPD* chronic obstructive pulmonary disease, *DPI* dry powder inhaler, *pMDI* pressurised metered-dose inhaler



introduces the potential for increased local adverse effects, which may also happen at a systemic level, as these agents have a long terminal half-life [16, 22]. As briefly reviewed in this section, budesonide's pharmacokinetic/pharmacodynamic properties make for a better balance between efficacy and safety than many of these newer ICS.

Budesonide is relatively less lipophilic, and hence more water soluble, than most other ICS [25, 67], which results in a shorter dissolution time in human bronchial fluid *in vitro* compared with other ICS (Table 1) [67, 71]. This allows it to enter the lung tissues quickly, minimising removal from the airways by mucociliary clearance or phagocytosis [67, 72, 73]. In contrast, very low water solubility with, for example, FF, MF and CIC (Table 1) prolongs the intraluminal dissolution time of these ICS and can extend their local anti-inflammatory efficacy [22]. However, such increased pulmonary residence time may also enhance the duration of the local immunosuppressive action of ICS in the airways/lung. This may be particularly important in the presence of impaired mucociliary clearance and altered lung microbiome in COPD, potentially increasing the risk of pneumonia [74, 75].

Absolute bioavailability, the drug taken up directly from airways/lung plus the swallowed and intestinally absorbed fraction bypassing the liver unmetabolised [22], is indicative of the potential for systemic distribution. Budesonide's absolute bioavailability is lower than that of BDP, and although it is greater than that of FLU, FP and MF (Table 2), several factors help to reduce the extent and duration of its systemic tissue absorption and its distribution. Firstly, it is cleared rapidly following systemic absorption—with a broadly similar clearance rate to FLU, FP and MF (Table 2) [22].

Secondly, ICS with higher lipophilicity have prolonged systemic elimination; the relatively lower lipophilicity of budesonide is thought to explain its shorter elimination half-life than that of FP, FF and MF (Table 1). Thirdly, in the systemic circulation, higher lipophilicity also results in a higher volume of distribution (V_d) which, along with prolonged systemic elimination, potentially results in drug accumulation in other body tissues and risk of more prolonged systemic exposure during repeated dosing (Fig. 3) [22, 37, 66, 76]. Budesonide's moderate lipophilicity is associated with a smaller V_d than, for example, CIC, FP, MF and FF (Table 2; Fig. 3) and therefore with shorter systemic exposure, contributing to a low risk of adverse events [15, 37, 39, 66].

4.1 Intracellular Pharmacodynamic Properties

After absorption into airway tissues, a considerable fraction of budesonide undergoes reversible intracellular esterification to produce highly lipophilic fatty acids in an inactive depot form (mainly budesonide-21-oleate) [77]. This occurs via lipid conjugation of budesonide's free hydroxyl group at carbon 21 (Fig. 4) [78]. Although lipid conjugation has also been observed with other ICS with a free hydroxyl group [22, 79], it is best documented for budesonide. As intracellular levels of free budesonide fall over time, these conjugates are hydrolysed by lipases, releasing more of the active drug to interact with the GCR [80]. It can be proposed that the esterification process therefore acts as a 'sustained-release' mechanism that prolongs lung residence time at the *intracellular* target level [80, 81]. This explains budesonide's high and extended local efficacy for a non-halogenated ICS with only moderate lipophilicity, in contrast with the more

Table 1 Properties of ICS

| Corticosteroid | Lipophilicity (log P) ^a [25] | Water solubility ^b (µg/mL) [25, 67] | Dissolution time (human bronchial fluid in vitro) [67] | Half-life (h) [22] | GCR binding affinity ^c [22, 25] | Selectivity for the GCR vs the PR [68] |
|--|---|--|--|--------------------|--|--|
| Beclometasone dipropionate | 4.59 | 0.13 | > 5 h | 0.1 | 53 | NA |
| 17-Beclometasone monopropionate ^d | 3.27 | 15.5 | ND | 2.7 | 1345 | 9.3 |
| Budesonide | 2.32 | 16 | 6 min | 2.8 | 935 | 44 |
| Fluticasone propionate | 3.89 | 0.14 | > 8 h | > 14 | 1775–1800 | 11.8 |
| Fluticasone furoate [69] | 4.17 | < 0.1 | NA | 17–24 [70] | 2989 ± 135 | NA |
| Mometasone furoate | 4.73 | < 0.1 | ND | 4.5 | 2100–2200 | 1.1 |
| Ciclesonide | 3.2 | < 0.1 | ND | 0.4 | 12 | NA |
| Desisobutyryl-ciclesonide ^e | 3.0 | 7 | ND | 3.6–5.1 | 1200 | NA |
| Flunisolide [69] | 1.36 | 140 | NA | 1.6 | 177 | NA |

GCR glucocorticoid receptor, ICS inhaled corticosteroids, NA not available in current literature, ND not determined, PR progesterone receptor

^aLog *p* values are defined as the log₁₀ of the octanol/water partition coefficient

^bWater solubility at 37 °C

^cRelative receptor affinity with reference to a receptor affinity of dexamethasone of 100

^dActive metabolite of beclometasone dipropionate

^eActive metabolite of ciclesonide

Table 2 Pharmacokinetic properties of ICS

| Corticosteroid | Absolute bioavailability ^a (%) [25] | Clearance (L/h) [22, 25] | Volume of distribution (L) [22, 25] | Protein-binding (%) [22, 25] |
|--|--|--------------------------|-------------------------------------|------------------------------|
| Beclometasone dipropionate | 82* | 120–230 | 20 | 87–96 |
| 17-Beclometasone monopropionate ^b | ND | 120 [†] | 424 [†] | NA |
| Budesonide | 39 [#] | 84 | 180–183 | 88–91 |
| Fluticasone propionate | 16 [#] | 69 | 318 | 90–99 |
| Fluticasone furoate [69] | 15 [#] | 65 | 608 | 99 |
| Mometasone furoate | 11 [#] | 54 | 332 | 98–99 |
| Ciclesonide | 63* | 152–228 | 207–396 | 99 |
| Desisobutyryl-ciclesonide ^c | ND | 396 [†] | 1190 [†] | 99 |
| Flunisolide [69] | 70* | 58 | 96 | 61–80 |

ICS inhaled corticosteroids, NA not available in current literature, MDI metered-dose inhaler, ND not determined

*Hydrofluoroalkane propellant MDI

[#]Dry-powder inhaler

[†]Apparent maximum approximation based on complete conversion of the parent compound

^aDetermined in healthy subjects

^bActive metabolite of beclometasone dipropionate

^cActive metabolite of ciclesonide

lipophilic ICS that are proposed to have extended airway residence due to their prolonged *intraluminal* dissolution time [77, 81]. Because the esterification process is driven by high budesonide concentrations, far fewer budesonide esters are formed within peripheral cells [78, 81, 82]. The ability of budesonide to undergo a reversible partial esterification

preferentially within airway cells is thought to create the unique ability to have a higher lipophilicity at the target tissue than when circulating in the body [78, 81, 83].

The binding affinity of ICS for the target GCR appears to be related to their lipophilicity, with budesonide having a considerably lower affinity than more lipophilic ICS such

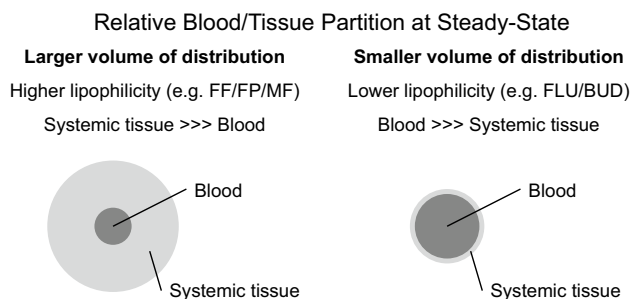


Fig. 3 Schematic diagram showing the difference in partitioning of high and low lipophilicity drugs between the hydrophilic (water soluble) blood compartment and the lipophilic (fat soluble) systemic tissue compartment and their total volume of distribution. *BUD* budesonide, *FF* fluticasone furoate, *FP* fluticasone propionate, *FLU* flunisolide, *MF* mometasone furoate

as MF, FP or FF (Table 1) [22]. However, a highly lipophilic inhaled ICS extends local tissue binding and GCR triggering [71], but when further distributed into the systemic circulation it may worsen the risk:benefit ratio due to its greater and longer systemic exposure [22].

Although budesonide has a lower GCR binding affinity, it offers the advantage of greater selectivity for the GCR versus the PR as compared with some other ICS (at least according to one study; Table 1); differences in GCR selectivity may be inversely related to lipophilicity [68]. This greater GCR versus PR selectivity may help avoid further systemic adverse effects, particularly at higher doses, when it is thought ICS may then also bind to the PR, which has a similar binding domain to the GCR [68].

4.2 Pharmacodynamic Rationale for ICS/ Long-Acting β_2 -Agonist (LABA) Combination Therapy

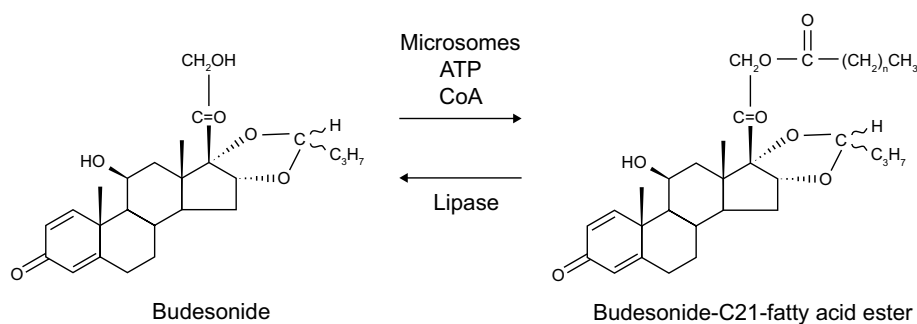
Numerous potential intracellular mechanisms of synergistic interaction between corticosteroids and β_2 -agonists have been identified [85]. Synergy has proved difficult to confirm in vivo, although additive effects have been demonstrated [41, 86–90], providing a rationale for the combination of

ICS and LABA for the treatment for asthma and COPD [85, 87, 91, 92]. Indeed, corticosteroids bind to a positive GRE and increase the gene transcription of β_2 -adrenoceptors in human lung tissue in vitro [93], thus increasing the expression of β_2 -receptors and protecting against their down-regulation and G-protein adenylyl cyclase uncoupling after long-term administration of β_2 -agonists [94–97]. There is also some evidence of activation of the GCR by β_2 -agonists which augments translocation of the bound GCR into the nucleus and may mediate the anti-inflammatory effect of ICS in vitro and in vivo [98, 99]. In addition, there is also evidence of ‘coincident pharmacology’ for ICS and LABA, resulting from a higher co-deposition on the same cells with the combined inhaler [85, 100]. This is supported by evidence of augmented ICS-induced GCR nuclear translocation in airway cells when an ICS is administered in combination with a LABA [98].

5 Budesonide Studies in Asthma

An abundance of data exists concerning budesonide treatment in patients with all severities of asthma. Budesonide 600 μg twice daily (bid) was compared with terbutaline 375 μg bid over 2 years in patients in whom asthma had appeared within the previous year [56]. Forced expiratory volume in one second (FEV_1), morning and evening PEF and asthma symptoms all improved with budesonide versus terbutaline, and the budesonide group also needed less ‘rescue’ terbutaline. These results supported early use of budesonide in newly detected asthma. A 1-year follow-up study to investigate the effect of reducing or discontinuing the steroid dose [57] from 1200 to 400 μg found that, compared with placebo, the lower budesonide dose maintained reduced bronchial hyperresponsiveness to histamine in 74% versus 33% of patients, with significant differences also seen in pulmonary function. A 2-year study with budesonide 400 μg bid and a 12-month study of early intervention with low-dose (200 μg bid) budesonide also supported early treatment with an ICS [60, 101]. Low maintenance doses of budesonide 100–200 μg bid have also proved effective in reducing severe

Fig. 4 Structural formulas of budesonide and budesonide-21-fatty acid esters [81, 84]. Reproduced with permission from Tunek et al. [84]



exacerbations and improving asthma control in patients with mild asthma [102].

The dose-dependent nature of budesonide's clinical efficacy was elucidated in a 12-week study in patients with moderate-to-severe asthma published in 1998 [63]. Budesonide was administered twice daily at a total dose of 200, 400, 800 or 1600 µg. The effects on PEF and FEV₁ were significantly greater with the 1600-µg dose than with the 200-µg dose, although not for the other doses studied. Flexible dosing with budesonide has also been investigated in patients with mild asthma [103]. Subjects were randomised to budesonide 200 µg bid, BDP 250 µg bid or non-steroidal treatment for 2 years, with the ICS dose adjusted according to asthma severity and treatment response. The patients receiving ICS had a more rapid and marked increase in FEV₁ and morning PEF compared with non-steroidal treatment, with the changes inversely correlated to mean ICS dose ($p < 0.001$).

The efficacy of budesonide in children has been investigated in several studies, notably the long-term Steroid Treatment As Regular Therapy (START) and the Childhood Asthma Management Program (CAMP) trials [104, 105]. The START study included 7241 patients, over a quarter of whom were children younger than 11 years [105]. Daily doses of budesonide 400 µg, or 200 µg for children, were compared with placebo. Budesonide significantly reduced the risk of a first severe asthma-related event by 44% (hazard ratio 0.56, 95% CI 0.45–0.71; $p < 0.0001$). There were also significant increases in pre- and post-bronchodilator FEV₁ and symptom-free days compared with placebo, supporting the use of long-term treatment with once-daily, low-dose budesonide in patients with recent-onset mild asthma. The CAMP study compared the efficacy of budesonide 200 µg bid and nedocromil sodium 8 mg bid with placebo for 4–6 years in 1041 children with mild-to-moderate asthma [104]. Budesonide treatment did not significantly increase post-bronchodilator FEV₁, although there were significant improvements in asthma symptoms, use of rescue medication, number of episode-free days and airway responsiveness to methacholine compared with placebo ($p \leq 0.01$). Efficacy has also been shown with nebulised budesonide (Pulmicort® Respules®) in children with steroid-dependent, persistent asthma [65].

6 Budesonide Studies in COPD

In the European Respiratory Society study on COPD (EUROSCOP), twice-daily budesonide 400 µg administered via DPI was compared with placebo over 3 years in patients with mild COPD who continued smoking [106]. The primary endpoint, change in post-bronchodilator FEV₁, improved with budesonide treatment in the first 6 months of

the study, but the changes from 9 months to the end of treatment were not significantly different. The median decline in FEV₁ over 3 years was 140 mL in the budesonide group and 180 mL with placebo ($p = 0.05$); or 4.3% and 5.3% of the predicted values, respectively ($p = 0.04$).

Nebulised budesonide has also been studied in COPD patients. In one study, budesonide 2 mg every 6 h for 72 h delivered by Pulmicort® Respules® was compared with oral prednisolone 30 mg every 12 h and placebo for the treatment of acute COPD exacerbations. Improvements in post-bronchodilator FEV₁ over 72 h were greater in both treatment groups versus placebo (budesonide versus placebo, 0.10 L [0.02–0.18]; prednisolone versus placebo, 0.16 L [0.08–0.24]), suggesting that nebulised budesonide could have value in treating acute COPD exacerbations [107].

7 Budesonide/Formoterol Studies in Asthma

Treatment with budesonide in combination with the fast-acting LABA, formoterol, has been extensively investigated in patients with asthma. In the FACET (Formoterol and Corticosteroids Establishing Therapy) study, the addition of formoterol to budesonide via separate inhalers significantly reduced mild and severe exacerbations compared with budesonide alone ($p < 0.01$). Mean symptom scores and rescue medication use were also significantly improved ($p < 0.001$) [90]. Similar results were obtained when patients received twice-daily maintenance therapy with budesonide/formoterol from a single inhaler [108]. A large real-world study using a retrospective matched cohort population database analysis showed lower rates of exacerbation and healthcare utilisation with the budesonide/formoterol combination than with salmeterol/fluticasone in asthma [109]. This combination treatment was first approved for use in asthma in 2001 and is currently available in a choice of pMDI or DPI devices. Budesonide/formoterol by DPI is also potentially suitable for once-daily dosing in patients with asthma, due to the long duration of action of both mono-components [81, 110].

8 Budesonide/Formoterol Studies in COPD

The budesonide/formoterol combination has also been investigated in patients with COPD. In two large, 12-month studies, twice-daily treatment with budesonide/formoterol 320/9 µg¹ delivered via DPI reduced the mean number of

¹ Delivered dose, corresponds to a budesonide/formoterol metered dose of 400/12 µg.

severe exacerbations versus all comparators ($p < 0.05$ versus formoterol) [111, 112], leading to the approval of this treatment in 2008 (not via DPI in the USA) for patients with COPD and a history of repeated exacerbations. In the 12-month SUN study [113], the higher strength budesonide/formoterol pMDI formulation (160/4.5 μg^2 bid) improved pre-dose FEV₁ and prolonged time to first COPD exacerbation versus formoterol ($p = 0.008$ and $p = 0.026$, respectively). Both budesonide/formoterol formulations (160/4.5 and 80/4.5 μg^3 bid) reduced the overall number of exacerbations per patient-treatment year versus formoterol (25% and 29%, respectively; $p \leq 0.004$). In the 6-month SHINE study [114], greater improvements in pre-dose FEV₁ and 1-h post-dose FEV₁ were observed with budesonide/formoterol 160/4.5 μg bid pMDI versus the primary comparators of formoterol ($p = 0.026$) and budesonide ($p < 0.001$), respectively. The recent RISE study compared budesonide/formoterol pMDI 320/9 μg bid with formoterol DPI 9 μg bid for 6 months in patients with moderate-to-very-severe COPD and a history of exacerbations [115]. Both the annual rate of moderate and severe exacerbations and the time to first exacerbation were significantly reduced with budesonide/formoterol treatment versus formoterol alone. The pMDI formulation of budesonide/formoterol 320/9 μg was approved by the US FDA for COPD in 2009 and for reduction of COPD exacerbations in 2017.

A number of other ICS/LABA DPI combination treatments have been approved for use in patients with COPD, but direct comparisons between these treatments are limited. In the retrospective, observational PATHOS study in matched patients with COPD, budesonide/formoterol was shown to significantly reduce the exacerbation rate versus salmeterol/FP (0.80 vs 1.09 exacerbations per patient-year) [116]. All other adverse healthcare outcomes were also significantly reduced with budesonide/formoterol. Similar results had been observed in another matched cohort population-based study in patients with COPD [117].

Due to the fast onset of bronchodilation with formoterol [118], budesonide/formoterol combinations can also be of benefit in patients with severe COPD who experience their worst symptoms in the early morning when lung function is at its lowest ebb, due to diurnal variation. In one study, short-term treatment with budesonide/formoterol 320/9 μg bid resulted in a significantly greater improvement in ability to perform morning activities ($p < 0.05$) than with salmeterol/fluticasone propionate 50/500 μg bid [119]. The CLIMB study showed that 12 weeks' treatment with the same dose of

budesonide/formoterol and the addition of tiotropium 18 μg once daily resulted in rapid and sustained improvements in morning lung function, symptoms, reliever use and activities and a 62% reduction in exacerbations versus tiotropium alone [120]. Interestingly, budesonide has been found to enhance the fast onset of action of formoterol in patients with stable COPD, possibly due to non-genomic actions that can occur within a few minutes [121].

9 Budesonide/Formoterol as Both Maintenance and Reliever Therapy in Asthma

Formoterol has a fast onset of bronchodilator effect similar to salbutamol [118], and although the bronchodilator effects last much longer than salbutamol, systemic effects are equally short-lived [122]. This enables more flexibility of dosing with a budesonide/formoterol combination than other ICS/LABA combinations where the LABA has a slower onset of effect and more prolonged systemic effects. The high water solubility and moderate lipophilicity of budesonide leads to dissolution in airway lining fluid within minutes, and subsequent rapid absorption into airway/lung tissue [22, 123]. One study has shown that, within 2 h of administration, a bolus dose of inhaled budesonide reverses subsensitivity to adenosine monophosphate bronchoprotection and associated down-regulation of lymphocyte β_2 -adrenoreceptors produced by regular formoterol treatment in patients with asthma [95]. The results from this study support the use of additional bolus doses of inhaled corticosteroids in conjunction with β_2 -agonists for the treatment of acute episodes of bronchoconstriction.

The use of budesonide/formoterol as an as-needed reliever with anti-inflammatory properties in addition to maintenance therapy provides an alternative to higher maintenance doses of ICS alone, and enables earlier, symptom-led intervention with ICS when patients experience worsening symptoms, potentially preventing the development of exacerbations (Fig. 5) [124, 125]. Regulatory approval outside of the US has been given for the budesonide/formoterol combination in a single DPI to be used in this way. This is a valuable additional approach to asthma management that fits in with how most patients actually behave, increasing reliever use when symptoms worsen [126, 127], whilst giving clinicians the reassurance that their patients will also receive an anti-inflammatory dose of budesonide with every dose of reliever.

To evaluate the specific contribution of as-needed budesonide/formoterol as a reliever against a background of maintenance therapy, the efficacy of three reliever strategies was investigated [128]. Patients with moderate to severe persistent asthma remaining symptomatic on budesonide/

² Delivered dose, corresponds to a budesonide/formoterol metered dose of 200/6 μg .

³ Delivered dose, corresponds to a budesonide/formoterol metered dose of 100/6 μg .

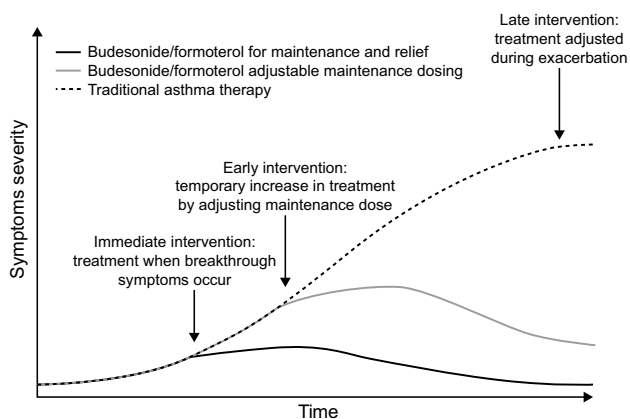


Fig. 5 Illustration of outcomes with different asthma treatment regimens in response to worsening symptoms [124]. Reproduced with permission from Ankerst [124]

formoterol maintenance therapy received terbutaline, formoterol or budesonide/formoterol as reliever medications for 12 months. Interestingly, both mono-components were shown to be important when given as needed in addition to budesonide/formoterol maintenance therapy, with formoterol reducing severe exacerbations to a greater extent than terbutaline. However, greater reductions in severe exacerbations were observed with budesonide/formoterol as both maintenance and reliever compared with formoterol as an as-needed reliever therapy on top of budesonide/formoterol maintenance treatment [128].

10 Safety

Inhaled corticosteroids have been associated with a risk of certain adverse events, such as pneumonia, oropharyngeal *Candida* infection and lower respiratory tract infections such as tuberculosis and non-tuberculous mycobacterioses. This is potentially due to immunosuppressive effects resulting from the relatively high local concentrations of these medications in the airways/lung [14, 129–132]. Systemic adverse effects can include reductions in bone mineral density (BMD), adrenal suppression, cataracts, and glaucoma [17, 103], as well as skin bruising [133]. A number of clinical trials and long-term studies have assessed the safety profile of budesonide and found the risk:benefit ratio to be favourable, both in asthma and COPD [39, 106, 134].

10.1 Safety in Asthma

In an analysis of asthmatic patient data from The Health Improvement Network database, budesonide use was associated with a small increase (odds ratio (OR) 1.20, 95% CI 1.06–1.35; $p=0.003$) in the risk of pneumonia or a

lower respiratory tract infection (LRTI), while the risk of these events was much greater with FP (OR 1.64, 95% CI 1.50–1.79; $p<0.001$) [129]. In the START study ($n=7241$) of early intervention in mild asthma, the frequency of infections was similar between budesonide and placebo (38.5% vs 38.3%) [39, 105], as was the incidence of tuberculosis (0.1% for placebo and 0.3% for budesonide) [39, 134].

The association of OCS with the development of osteoporosis is well documented, but the effect of ICS on bone metabolism and bone density is less clear [103]. In a long-term study of inhaled budesonide in children with asthma, there were no adverse effects on BMD, total bone calcium, total body bone mineral capacity or body composition after 3–6 years of treatment. The mean daily budesonide dose was 504 μg , and there was no correlation between duration of treatment and bone density parameters [135]. When changes in BMD were compared between ICS and non-ICS treatments over 2 years in adults with mild asthma, no significant differences were observed between budesonide, BDP or a non-steroid reference treatment [103]. There was a correlation between ICS dose and a reduction in BMD at the lumbar spine over the 2-year study, possibly due to a direct effect on bone or to an indirect effect related to asthma severity, but overall the data suggest that low to moderate doses of ICS have little effect on BMD over 2 years. A 1-year, open-label study in 59 adult patients with moderate-to-severe asthma reported no significant difference between high-dose budesonide and high-dose FP in BMD, and no significant decline in BMD overall [136].

The systemic potency of ICS can be measured by their effects on the hypothalamic–pituitary–adrenal (HPA) axis, and a number of long-term trials have studied this [39]. HPA axis function was one of the safety endpoints in a 52-week, open-label study of budesonide (100–800 μg bid) in adults and children [137]. There was no evidence of any suppression in function, as both basal and stimulated plasma cortisol levels were maintained throughout the study. These results were reflected in two further studies in children on long-term budesonide treatment, with one study even showing improvements in adrenal function with budesonide over 6–12 months [138, 139]. Budesonide has also been shown to have a minimal effect on serum cortisol levels and bone turnover in comparison with microgram-equivalent doses of FP [17, 140–143].

A long-term study of children with mild-to-moderate asthma by the CAMP Research Group assessed the effect of ICS on lung function and growth over 4–6 years [104]. Children receiving budesonide 200 μg bid showed no significant difference in lung function versus placebo at 4 years, as measured by change in post-bronchodilator FEV₁, despite an improvement at 1 year. The budesonide group showed a small, transient reduction in growth velocity versus placebo, primarily evident within the first year. However, growth

velocity was similar by the end of the treatment period, and changes in bone density and end-of-treatment bone age, projected final height and Tanner stage were all similar to placebo. The growth velocity findings were supported by an 18-month study of continuous low-dose budesonide or continuous budesonide for 6 months then as needed [144]. A small initial decline in growth velocity with both budesonide treatment regimens normalised by the end of the trial, with budesonide as-needed associated with catch-up growth. No long-term adverse effects on growth velocity or weight gain were seen in further studies in asthmatic children with daily budesonide doses of up to 400 µg [59]. While a meta-analysis in children with mild-to-moderate persistent asthma found greater reductions in 1-year mean linear growth velocity with budesonide than with several other ICS (CIC, FLU, FP and MF) using indirect comparison methods, the differences were small (−0.59 versus −0.08 to −0.47 cm/year) and their clinical relevance was not clear [145].

Other systemic adverse effects linked to the long-term use of high-dose ICS include cataracts, glaucoma, and ocular hypertension [17]. However, two studies in children with asthma found no increase in occurrence of posterior subcapsular cataracts versus controls after up to 6 years' treatment with budesonide [104, 146].

Data from large-scale retrospective studies have shown that treatment with anti-asthmatic medications can increase the risk of pregnancy complications and low infant birth weight [147, 148], although budesonide-specific data have not shown a significant increase in congenital malformations [39, 149]. A study in pregnant mice showed less transplacental transfer of free budesonide than of free FP [150]. This appeared to depend on the lower lipophilicity of budesonide and the fact that, as a substrate for P-glycoprotein, budesonide can be transported out of the placenta and brain.

10.2 Safety in COPD

An increased incidence of pneumonia in COPD patients receiving ICS treatment has been observed in several studies, although there are indications of intra-class differences in risk [75, 151, 152]. Recent studies in human bronchial epithelial cells have shown that treatment with budesonide results in significantly higher expression of specific immune defence genes, and greater airway epithelial barrier protection against cigarette smoking and viral infection, than treatment with FP [31, 75, 153]. Due to its greater lipophilicity and tenfold higher immunosuppressant potency, the prolonged residency time of FP in the airway epithelial lining fluid compared with budesonide may result in an increased duration of local immunosuppression and impaired pathogen clearance from the airways [14, 75, 154]. Additionally, very recent work has demonstrated a differential response to budesonide compared with FP in blood-derived

macrophages in smokers and ex-smokers with COPD [155]. Budesonide counteracted reductions in bacterial recognition receptors on monocyte-derived macrophages by both non-typeable *Haemophilus influenzae* and *Streptococcus pneumoniae*, whereas FP only counteracted some of the reductions by *S. pneumoniae*. These differences may provide a greater understanding of mechanisms by which patients taking fluticasone-based preparations for COPD tend to be more susceptible to pneumonia [14]. The European Medicine Association's Pharmacovigilance Risk Assessment Committee reviewed the known risk of pneumonia with ICS in 2016 and concluded that, although COPD patients treated with ICS are at increased risk of pneumonia, the benefits of ICS continue to outweigh their risks [156]. In a population-based cohort study of patients with COPD, budesonide was associated with a comparatively much lower risk of pneumonia (17% increased risk with no dose-response effect) than FP (dose-dependent increase, with the 1000-µg dose associated with a 122% increase in risk) or other ICS (primarily BDP) [74]. A meta-analysis of 43 studies made indirect comparisons of budesonide and fluticasone monotherapy and found a higher risk of any pneumonia event with fluticasone than with budesonide (OR 1.86, 95% CI 1.04–3.34), although between-group differences were not significant for non-fatal serious adverse pneumonia events or mortality [157]. The authors cautioned interpretation of these results due to the quality of evidence and the indirect nature of the comparison [157]. In the FULFIL study, the rate of pneumonia in patients with COPD was lower with twice-daily budesonide/formoterol than with a once-daily triple therapy of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) [158]. The incidence of pneumonia, a pre-specified adverse event of special interest, over 24 weeks in the intention-to-treat population was 2.2% with FF/UMEC/VI versus 0.8% with budesonide/formoterol. Additionally, in the PATHOS study, budesonide/formoterol was associated with a significantly lower rate of pneumonia and hospital admission for pneumonia (both $p < 0.001$) than salmeterol/FP in matched cohorts of patients with COPD [14]. The risk of pneumonia was not associated with the dose of ICS received for either treatment. The 6-month KRONOS trial showed similar rates of confirmed pneumonia (2%) for both budesonide/glycopyrrolate/formoterol and glycopyrrolate/formoterol [159].

A meta-analysis of seven large clinical studies concluded that treatment with budesonide for 12 months does not increase the risk of pneumonia in patients with COPD as compared with control (formoterol or placebo) [160]. A subsequent meta-analysis that included an eighth large trial found that the incidence of pneumonia increased with increasing severity of airflow limitation, both for patients who received budesonide and those on non-ICS controls [161]. However, although this further trial showed a

significantly increased pneumonia incidence with budesonide/formoterol compared with formoterol alone, when these data were added to the pooled data from the seven trials, no significantly increased risk of pneumonia with budesonide was noted [162]. Although the overall risk for pneumonia increased with COPD severity, there was no difference in pneumonia risk with budesonide treatment in any Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity group. In the RISE study, the incidence of protocol-defined pneumonia or LRTI adverse events was numerically lower with budesonide/formoterol (pneumonia, 0.5%; LRTI, 1.5%) than with formoterol alone (pneumonia, 1.0%; LRTI, 3.3%) [115]. No patients in the budesonide/formoterol group experienced pneumonia as a serious adverse event, compared with 0.8% of patients in the formoterol group. A pooled analysis of 11 interventional studies, which included > 10,000 patients, compared the difference in pneumonia risk between inhaled budesonide-containing and non-budesonide-containing treatments [163]. The risk of pneumonia treatment-emergent adverse events (TEAEs) or serious adverse events (TESAEs) was not significantly increased with budesonide-containing compared with non-budesonide-containing treatments (pooled HR 1.13 and 1.15, respectively). The annual incidence rates with budesonide- and non-budesonide-containing products were similar (5.2% vs 4.6%, respectively, for TEAEs and 1.9% vs 1.5% for TESAEs).

As in asthma, changes in BMD have also been observed in clinical trials in COPD patients. In the 3-year, placebo-controlled EUROSCOP study, budesonide 400 µg bid had no significant effect on BMD, apart from a small positive effect on femoral trochanter bone density yearly decline (0.04% for budesonide vs 0.38% for placebo; $p=0.02$) [106]. The 12-month SUN trial found small but significant decreases in total lumbar spine and total hip BMD with budesonide/formoterol 320/9 µg versus formoterol 9 µg, as seen on dual energy X-ray absorptiometry (DEXA) scans, but the clinical relevance of these findings was unclear [113]. Of note, ophthalmology assessments were also performed in the SUN trial, including intraocular pressure and lenticular opacities. Similar minor increases in these parameters were observed across all treatment groups. Budesonide/formoterol 320/9 µg was associated with a small increase from baseline in posterior subcapsular score compared with budesonide/formoterol 160/9 µg ($p=0.022$), but other clinically significant ophthalmological changes were infrequent [113].

11 The Future Role of ICS in Airways Disease

Historically, ICS clinical trials have not been selective for specific asthma phenotypes. However, current guidelines acknowledge asthma as a heterogeneous condition, with

several phenotypes now recognised. The treatable allergic asthma phenotype is often associated with an eosinophilic airway inflammation endotype. These patients usually respond well to ICS treatment, and treatment guided by sputum eosinophil count is associated with a reduced risk of exacerbations compared with guidelines-based treatment [18]. Existing biomarkers such as blood eosinophil count, levels of nitric oxide in exhaled breath (FeNO) and serum immunoglobulin E, in addition to developments in new biomarkers and tools for personalised medicine, will play an increasing role in asthma management in the future [164].

The use of ICS/LABA combination therapy in patients with asthma is evolving. While it has traditionally been viewed as controller therapy, the potential of using this combination alone as an as-needed reliever in mild asthma has now been investigated in the two SYGMA (SYmbicort Given as needed in Mild Asthma) studies [165, 166]. In SYGMA 1, the severe exacerbation rate was reduced by 64% with as-needed budesonide/formoterol versus terbutaline (annualised exacerbation rates 0.07 and 0.20, respectively; rate ratio (RR) 0.36), and was not significantly different from that of budesonide maintenance plus as-needed terbutaline as reliever (annualised exacerbation rates 0.07 and 0.09, respectively; RR 0.83). Superiority to terbutaline and equivalence to budesonide maintenance plus terbutaline were also seen in time to first severe exacerbation. Glucocorticoid exposure was substantially lower with as-needed budesonide/formoterol than with budesonide maintenance in both studies: the median metered daily ICS dose was 83% lower in the budesonide/formoterol group compared with the budesonide maintenance group in SYGMA 1 (57 µg and 340 µg, respectively) and 75% lower in SYGMA 2 (66 µg and 267 µg, respectively). Together, the SYGMA studies showed that as-needed budesonide/formoterol was superior to as-needed short-acting β_2 -agonist (SABA) alone for asthma symptom control and exacerbation risk reduction in mild asthma. The 2019 update to the Global Initiative for Asthma (GINA) report now recommends use of as-needed ICS/formoterol for patients on treatment step 1, replacing SABA as first-line reliever for safety reasons, because SABA has no anti-inflammatory effect and may in fact worsen eosinophilic airway inflammation [167].

GINA now proposes that asthma patients move from as-needed ICS/formoterol only as a reliever up to ICS/formoterol as both maintenance therapy and as-needed reliever therapy, providing a treatment continuum across the spectrum of mild to moderate to severe asthma, with inherent flexibility of dosing and symptom control [167]. Hence, patients may intuitively step up and step down according to asthma control in a personalised flexible dosing regimen—in other words, use more when needed and less when not (Fig. 6).

Continuum of treatment with budesonide/formoterol for mild-moderate asthma

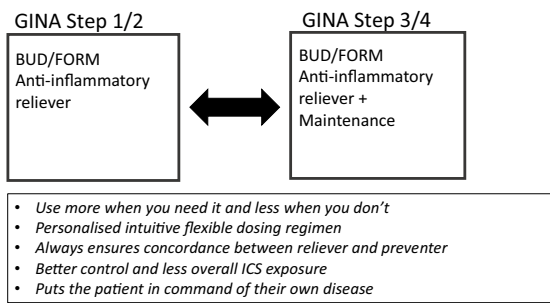


Fig. 6 The continuum of treatment with budesonide/formoterol for mild to moderate asthma. *BUD* budesonide, *FORM* formoterol, *GINA* Global Initiative for Asthma, *ICS* inhaled corticosteroid

Budesonide/formoterol is currently the only ICS/LABA licenced for this type of use, although this was because these components were well suited to each other in terms of their rapid uptake and short latency time, whereas most later ICS/LABA combinations were aimed instead at a longer duration of action. By always assuring concordance between budesonide and formoterol in this way, patients will automatically receive their ICS whenever they feel the need to take their reliever therapy. This is not the case with fixed-dose administration of combination ICS/LABA plus SABA reliever regimens, where many patients may stop or adhere poorly to their ICS/LABA and over-rely on their SABA reliever [168, 169].

As in asthma, ICS have generally only been tested in a broad COPD population. However, high levels of peripheral blood eosinophils have been reported in a significant proportion of patients with COPD [170], and appear to be predictive of clinical benefit from ICS or ICS/LABA. They may, therefore, have utility in determining which patients with COPD should receive ICS as part of their treatment regimen [21, 170, 171].

Some patients with advanced COPD benefit from triple therapy with an ICS/LABA in combination with a long-acting muscarinic antagonist, and this approach is one of the suggested treatment pathways in the latest GOLD guidelines for Group D patients experiencing further exacerbations [21]. The TRIBUTE study showed an overall 15% reduction in moderate to severe exacerbations and no increase in pneumonia with beclomethasone/formoterol/glycopyrronium versus indacaterol/glycopyrronium [172]. The IMPACT study showed 15% and 25% reductions in exacerbations with fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/vilanterol and umeclidinium/vilanterol, respectively. There was a 53% higher risk of pneumonia with triple therapy versus umeclidinium/vilanterol, and a similarly increased pneumonia risk with fluticasone furoate/vilanterol [173]. The KRONOS study in moderate to very severe COPD (mostly GOLD group B) showed significantly

improved FEV₁ area under the concentration-time curve from 0 to 4 h (AUC₀₋₄) with budesonide/glycopyrrolate/formoterol treatment compared with budesonide/formoterol pMDI and DPI dual combination therapies (both $p < 0.0001$) [159]. The change from baseline in morning pre-dose trough FEV₁ was also significantly improved with triple therapy compared with glycopyrrolate/formoterol ($p = 0.0139$) and budesonide/formoterol pMDI and DPI (both $p < 0.0001$). Furthermore, there were significant improvements in secondary lung function endpoints compared with budesonide/formoterol, as well as a 52% reduction in moderate or severe exacerbations compared with glycopyrrolate/formoterol (model-estimated annual RR 0.48, 95% CI 0.37–0.64; $p < 0.0001$). Pneumonia incidence was low (<2%) and similar across treatments [159].

12 Conclusions

Many patient-years of clinical experience have been accumulated with budesonide, providing a wealth of evidence of its efficacy and safety profile. Its molecular structure gives budesonide unique pharmacokinetic and pharmacodynamic properties that differentiate it from other ICS. The relatively low lipophilicity and high water solubility of budesonide compared with other ICS allows quicker absorption into lung tissue. The resultant lower volume of distribution, combined with a rapid systemic elimination, is responsible for the low risk of adverse events observed with budesonide in clinical use. The differentiating ability of budesonide to undergo a partial esterification of its free hydroxyl group at carbon 21 increases lipophilicity at the target tissue, prolonging its duration of action at the GCR and extending its airway efficacy and selectivity [83, 174].

Among current ICS, budesonide is the most versatile due to its dose-response relationship, including the possibility of administration by nebulisation to infants or the infirm elderly and in an intensive-care setting. Budesonide as a single-drug formulation has proven efficacious as maintenance therapy in both adults and children across a range of asthma severities, with positive results in studies with early intervention, low-dose and flexible-dose regimens. Increased efficacy with the addition of formoterol via a separate inhaler was followed by the introduction of fixed-combination budesonide and formoterol. The fast onset of bronchodilator action with formoterol, combined with the favourable pharmacokinetic properties of budesonide, makes this combination well suited for as-needed use with or without regular maintenance therapy in patients with asthma. This approach ensures treatment with ICS as soon as symptoms worsen. The fast and effective symptom relief provided by budesonide/formoterol is also of benefit to patients with COPD, improving their ability to perform morning activities while the sustained

effects improve breathlessness throughout the day with twice-daily dosing [119]. In addition, budesonide may be associated with a lower risk of pneumonia than FP or FF in patients with COPD [74].

The recent SYGMA studies showed the superior efficacy of as-needed budesonide/formoterol to as-needed SABA in terms of reducing the risk of exacerbation and improving symptom control in mild asthma. With comparable reductions in exacerbations to budesonide maintenance therapy, but with a lower ICS treatment load and no clinically relevant difference in asthma control, the results support the use of a reliever with anti-inflammatory properties as a flexible and intuitive treatment for mild asthma that accommodates the typical behaviour patterns of patients and improves the benefit:risk ratio of asthma treatment.

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Compliance with Ethical Standards

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Conflict of interest Donald Tashkin has been the recipient of research grant support and fees for speaking and serving as a scientific advisory board member for AstraZeneca, an advisory board member and speaker for Teva, an advisory board member for Innoviva, the recipient of research grant support and an advisory board member for Novartis and a speaker and advisory board member for Sunovion. Brian Lipworth has received support from AstraZeneca for attending ATS 2018 as well as consultancy payments. He has also received payments for speaking, consulting, or advisory boards with Chiesi, Novartis, Sandoz, Sanofi, Teva, Lupin, Genentech, Boehringer Ingelheim, Dr. Reddy's, Cipla, Vectura and Glenmark. Support for unrestricted grants or multicentre trials has been received from AstraZeneca, Teva, Janssen and Chiesi. Equipment and educational support provided by GlaxoSmithKline. Ralph Brattsand is a former employee of Astra and AstraZeneca but today is without economic support from them. He was one of the key inventors of budesonide, and holds stocks with AstraZeneca.

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