

EXPERT
REVIEWSInhaled corticosteroids for
asthma: on-demand or
continuous use*Expert Rev. Respir. Med.* 7(6), 687–699 (2013)**Neil C Thomson* and
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Continuous inhaled corticosteroid treatment is highly effective in children and adults with mild persistent asthma, although some therapeutic benefits are not lost if treatment is delayed. Many patients do not adhere to continuous treatment with inhaled corticosteroids, but rather take them intermittently, usually at the time of increased symptoms. Based on these observations it has been proposed that for patients with mild persistent asthma inhaled corticosteroids should be used on-demand when symptoms are troublesome, rather than on a continuous basis. The article reviews the pharmacological properties of inhaled corticosteroids used in clinical trials of on-demand treatment, as well as the evidence for the efficacy and safety of on-demand compared with continuous inhaled corticosteroid treatment of mild persistent asthma in adults and children. The place of on-demand treatment with inhaled corticosteroids in the management of asthma is discussed, as well as future directions for different management strategies for this group.

KEYWORDS: anti-inflammatory • asthma • beclomethasone • budesonide • budesonide Turbuhaler® • hydrofluoroalkane • HFA-BDP Clenil® Modulite® • HFA-BDP Qvar® • inhaled corticosteroid

Asthma is a chronic inflammatory disease of the airways that affects 300 million people worldwide, with over half this population having mild intermittent or persistent asthma [1]. Both national and international guidelines recommend that daily inhaled corticosteroid is the preferred treatment option for children and adults with mild persistent asthma [201, 202] as inhaled corticosteroids improve asthma control and lung function as well as reduce exacerbation rates [2,3]. However, surveys of patient attitudes to asthma treatment and analysis of pharmacy records indicate that many patients do not adhere to regular treatment with inhaled corticosteroids, but instead take them intermittently, usually at the time of increased symptoms [4,5]. Interestingly, a 5-year follow-up of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) trial reported that delaying treatment with inhaled corticosteroids for 3 years in patients with recent onset asthma resulted in the same clinical benefits as those who commenced treatment at an earlier stage [6]. Thus, the absence of continuous

inhaled corticosteroid treatment may not result in impaired lung function over time in patients with mild asthma, although this observation may not apply to those with more severe disease. Based on these observations it has been proposed that the administration of inhaled corticosteroids on-demand when asthma symptoms are troublesome rather than on a continuous basis may be an effective treatment strategy for mild persistent asthma [7]. This article reviews the pharmacological properties of the inhaled corticosteroids used in clinical trials of on-demand regimens as well as evaluating the evidence for the efficacy and safety of on-demand, compared with continuous inhaled corticosteroid treatment of mild persistent asthma in adults and children with asthma. The place of on-demand treatment with inhaled corticosteroids in the management of asthma is discussed as well as future directions for treatment of mild persistent asthma.

**Mode of action of inhaled
corticosteroids**

Corticosteroids are the most effective treatment for asthma through their inhibitory

Table 1. Pharmacokinetic properties of an ideal inhaled corticosteroid.

Improved efficacy	Improved safety
High pulmonary deposition	Low oral bioavailability
Small particle size	High plasma protein binding
High pulmonary bioavailability	Rapid systemic clearance
High corticosteroid receptor binding affinity	Low oropharyngeal deposition
High on-site activation in the lung	On-site activation in the oropharynx
Prolonged lung residual time	
Data taken from [19,20].	

actions on inflammatory cells and pathways involved in the pathogenesis of the disease [8]. Corticosteroids reduce inflammation through activation of glucocorticoid receptors in the cytoplasm of target cells. The activated glucocorticoid receptor–corticosteroid complex binds to glucocorticoid-responsive elements (GREs) in the promoter region of corticosteroid-responsive genes within the nucleus to suppress (transrepression) or induce (transactivation) glucocorticoid target genes. Transrepression is believed to be responsible for the majority of the anti-inflammatory activity of corticosteroids through the reduced synthesis of pro-inflammatory transcription factors and by preventing their stimulation of inflammatory genes. The molecular mechanisms for the anti-inflammatory effects of corticosteroids are complex and not fully elucidated [9,10]. However, a key mechanism is thought to involve the reversal of histone acetylation of activated inflammatory genes through ligand-bound glucocorticoid receptors binding to co-activator molecules and subsequent recruitment of histone deacetylase (HDAC)-2 to the activated inflammatory gene transcription complex [8]. Recent studies suggest that the production of anti-inflammatory proteins may have a more important role in resolution of inflammation than previously considered [9,10]. Corticosteroids induce histone acetylation of anti-inflammatory genes (transactivation), including mitogen-activated protein (MAP) kinase phosphatase 1 (MKP-1) and glucocorticoid-inducible leucine zipper 1 (GILZ-1) as well as potentiating the effects of β_2 -agonists, in part through increased expression of β_2 -adrenergic receptors on cell surfaces [8]. The adverse effects of corticosteroids are thought to be due to transactivation of genes involved in glucose, lipid and muscle metabolism as well as by interacting with negative GREs to inhibit the production of osteocalcin, which is involved in bone synthesis [8]. Corticosteroids may also exert anti-inflammatory effects through a non-genomic mechanism, which has a rapid onset within minutes, is of short duration and is dose-dependent [11]. The mechanism is thought to be due to non-specific interactions of corticosteroids with the cell membrane. The combination of inhaled corticosteroids with short-acting and/or long-acting β_2 -agonists may also enhance the molecular actions of corticosteroids in reducing inflammation [12,13] and airway remodelling [14] by several possible

mechanisms, including increased translocation of the glucocorticoid receptor–corticosteroid complex from the cytoplasm to the nucleus [15] and by increased HDAC activity [13].

Pharmacokinetics & pharmacodynamics properties of inhaled corticosteroids

A favorable therapeutic index for an inhaled corticosteroid depends on a balance between efficacy outcomes and systemic adverse effects, which are both influenced by the pharmacokinetics and pharmacodynamics of the compound. These properties have been reviewed in detail previously [16–20]. Pharmacokinetic factors that improve efficacy include good pulmonary deposition, small particle size, high pulmonary bioavailability, good corticosteroid receptor binding affinity as well as high on-site of activation in the lung and prolonged lung residence time, whereas systemic adverse effects are reduced by low oral bioavailability, high plasma protein binding and rapid systemic clearance of the inhaled corticosteroid (TABLE 1). Pharmacokinetic factors that improve efficacy such as high pulmonary bioavailability and high receptor binding affinity can have an unfavorable impact on systemic adverse effects of inhaled corticosteroids. The pharmacokinetics and pharmacodynamics of inhaled corticosteroids used to date in clinical trials of continuous versus on-demand dosing strategies are summarized below, namely budesonide and beclomethasone.

Budesonide

The dry powder formulation of budesonide (Turbuhaler®, AstraZenica), inhaled in an active form, has a particle size of 3 μm and lung deposition of 22%, predominantly in the central airways (TABLE 2) [21]. The dose of budesonide inhalation suspension (Pulmicort® Respules® 0.5 mg) administered to a patient depends on the nebulizer equipment used as well as flow rate, volume of nebulizer, fill volume and air-flow rate.

Beclomethasone

Beclomethasone dipropionate (BDP) is a pro-drug with weak glucocorticoid receptor binding affinity, which is converted by esterase enzymes to the active metabolite beclomethasone-17-monopropionate (BMP). Chlorofluorocarbon (CFC) was the propellant previously used to deliver BDP until replaced by hydrofluoroalkane (HFA). Two formulations of BDP with a HFA propellant are marketed in different countries as pressurized metered-dose inhalers, namely, HFA-BDP Qvar®, TEVA and HFA-BDP Clenil® Modulite®, Chiesi (TABLE 2). Both formulations are in solution, which favors greater lung deposition than inhaled corticosteroids formulated in suspension [18,22]. HFA-BDP Qvar compared with HFA-BDP Clenil Modulite has a smaller particle size (mass median aerodynamic diameter (MMAD) 1.1 vs 2.6 μm) and achieves greater lung deposition (55–60 vs 36%) and because of these differences the equivalent dose of HFA-BDP Qvar is considered to be half that of HFA-BDP Clenil Modulite. For comparison, the MMAD and lung deposition of previously marketed CFC-BDP from a pressurized metered-dose inhaler was 3.5 μm and 8%, respectively.

Table 2. Pharmacokinetic properties of selected inhaled corticosteroids.

Pharmacokinetic property	HFA-BDP (Qvar [®]) pMDI	HFA-BDP (Clenil [®] Modulite [®]) pMDI	Budesonide Turbohaler [®]	HFA-Fluticasone propionate pMDI
Formulation	Solution	Solution	Dry powder	Suspension
Pulmonary deposition (%)	55–60	36	22	16
Particle size (MMAD, μm)	1.1	2.6	3	2.6–2.8
Receptor-binding affinity (relative to dexamethasone = 100)	1345 (BMP)	1345 (BMP)	935	1800
Oral bioavailability (%)	26	26	11–14	<1
Protein binding (%)	94–96 (BMP)	87	85–90	90
Clearance (l/h)	120 (BMP)	120 (BMP)	84	69
Elimination half-life (h)	2.8 (BMP)	2.7 (BMP)	2–3	14.4

BDP: Beclomethasone (beclometasone); BMP: Beclomethasone 17-monopropionate; HFA: Hydrofluoroalkane; MMAD: Mass median aerodynamic diameter; pMDI: Pressurized metered-dose inhaler.
Data taken from [17,18,19,21,45,54,85].

Both formulations of HFA-BDP containing pressured metered-dose inhalers have improved total and peripheral lung distribution compared with inhaled dry powder budesonide and inhaled HFA-fluticasone propionate (TABLE 2) [23].

Small airway deposition of HFA-beclomethasone

Airway inflammation and remodeling in asthma involves both the large and small airways in mild, as well as severe asthma [24–26]. The development of inhaled corticosteroids with extrafine-particle size and improved peripheral airway deposition has contributed to a reawakened interest in the role of small airway dysfunction in asthma and as a target for inhaled corticosteroid treatment [27]. Dysfunction of small airways (defined as diameter <2 mm) may contribute to poor asthma control in adults and children with asthma including patients with mild disease [26–31]. Recent studies have investigated whether treating the small airways with extrafine-particle inhaled corticosteroids improves clinical outcomes of asthma control to a greater extent than with large-particle inhaled corticosteroids [27–32]. Small particle size pressured metered-dose inhalers may potentially impact favorably on the safety and efficacy of inhaled corticosteroids through improved total lung deposition, resulting in asthma control at lower daily doses than the large-particle inhaled corticosteroid perhaps by treating small airway inflammation [19,20]. Observational studies in the UK and USA suggest that extrafine particle HFA-BDP Qvar may achieve better control at lower prescribed doses than large particle inhaled corticosteroids [33–36], but to date it has not been clearly demonstrated that equipotent doses of small-particle inhaled corticosteroids compared with large-particle inhaled corticosteroids either improve efficacy or reduce systemic adverse effects [19,27,37].

Dose-response to inhaled corticosteroids

Systematic reviews of dose-response clinical trials of inhaled corticosteroids in adults and children with asthma have

demonstrated that most of the therapeutic benefit is achieved with low to medium doses [38–44]. Therefore, for most patients with mild persistent asthma an effective dose in children is 200 μg daily and in adults 400 μg daily, although higher doses may be required in those with severe disease [18,39,40]. The dose-response curve for efficacy outcomes is moved to the left with HFA-BDP Qvar [45] due to the small particle size and greater lung deposition of this formulation. In contrast to the dose-response relationship for efficacy outcomes, inhaled corticosteroids exhibit a more linear relationship for systemic adverse effects with no plateau in response [38,46]. High doses of inhaled corticosteroids have the potential for systemic adverse effects such as adrenal suppression [18,39,43,46–48], reduced growth velocity in children [44,49,50] and reduction in bone mineral density as well as increased likelihood of fractures and osteoporosis [17,51]. Inhaled HFA-BDP Qvar administered at doses of 200, 400 or 800 μg daily to adults with corticosteroid-naïve asthma produces a non-significant 12.2% reduction in 24-h urinary-free cortisol at the 200 μg daily dose [45,52]. In children with asthma, inhaled HFA-BDP Clenil administered at doses of 400 μg daily does not suppress adrenal function [53] and in adults the effects are similar to CFC-BDP [54]. The safety profile of extrafine-particle inhaled corticosteroids on growth velocity in children and on the HPA axis appears to be similar to that of large particle inhaled corticosteroids and some studies suggest that there may be higher systemic bioavailability with smaller particles inhalers [19]. Local adverse effects such as oral candidiasis and hoarseness occur more frequently for some inhaled corticosteroids at high doses, such as fluticasone propionate [43], but are uncommon at low-to-moderate doses [44]. The smaller particle size of BDP-HFA Qvar[®] results in reduced oropharyngeal deposition (35%) compared with a large-particle inhaler such as HFA-fluticasone-salmeterol combination (77%) [22]. Taken together, these findings suggest that low to medium doses of continuous inhaled

Table 3. Potential factors influencing an individual's therapeutic response to inhaled corticosteroids in asthma.**Genetic**

- Glucocorticoid receptor polymorphisms
- TBX21 polymorphisms
- CRHR1 polymorphisms

Environmental

- Cigarette smoking
- Allergen exposure
- Infection

Asthma-related factors

- Adherence
- Inhaler technique
- Duration and severity of asthma
- Airway inflammatory cell phenotype
- Corticosteroid-resistant asthma
- Concomitant disease and misdiagnosis

Demographic factors

- Age, gender and race
- Body mass index

CRHR1: Corticotrophin-releasing hormone receptor 1.
Data taken from [55].

corticosteroids used in on-demand versus continuous dosing strategies are safe and effective in children and adults with mild persistent asthma.

Additional factors that influence the therapeutic response to inhaled corticosteroids

There is a variable therapeutic response to inhaled corticosteroids in asthma due to factors other than the pharmacological properties of the drug (TABLE 3) [55]. Non-adherence with inhaled corticosteroid therapy is one of the most important factors accounting for poor asthma control [4]. While the extent of deposition within the lungs is influenced by the delivery device used, the adequacy of the patient's inhaler technique and inspiratory flow [18,56,57], in patients with a poor inhaler technique a larger dose of extrafine-particle size HFA-BDP from a metered-dose inhaler is deposited in the lung (>37%) compared with larger-particle size CFC-BDP from a metered-dose inhaler (4–7%) [58]. Other factors include an eosinophilic airway phenotype, which is associated with an improved response to inhaled corticosteroids [59] and cigarette smoking [60], high basal metabolic index (BMI) [61] and some genetic factors [62] as well as severe disease [63] which are associated with reduced sensitivity to inhaled corticosteroids. The particle size of HFA-BDP is increased in the presence of tobacco smoke and based on this finding it has been postulated that cigarette smoking could prevent the dispersion of corticosteroid into the small airways of the lung and hence inhaler efficacy [64].

Clinical trials of on-demand compared with continuous use of inhaled corticosteroids

Currently licensed inhaled corticosteroids are effective when administered twice daily in asthma. There is also evidence that in some patients with mild persistent asthma, once-daily

administration is sufficient to achieve control [65]. There are a number of long-acting inhaled corticosteroids under development that should allow once-daily administration for more severe groups of patients [66]. Several clinical trials have assessed the efficacy and safety of employing currently available corticosteroids in an on-demand versus daily basis in persistent asthma in children and adults in clinical trials lasting up to 1 year (TABLE 4). A systematic review of six clinical trials including 1211 participants with mild persistent asthma has been recently reported [67]; two studies were in adults [68,69] and four studies in children, two studies in pre-school children [70,71] and two studies in school-aged children [72,73]. The meta-analysis concluded that on-demand and conventional daily inhaled corticosteroid strategies were similarly effective in the requirement for rescue courses of oral corticosteroids (relative risk (RR) 1.07; 95% confidence interval (CI): 0.87–1.32) (FIGURE 1) and the rate of severe adverse health events (RR 0.82; 95% CI: 0.33–2.03) (FIGURE 2). The improvements in peak expiratory flow (PEF) (2.56%, 95% CI: -4.49 to -0.63%), asthma control days (-9%, 95% CI: -14 to -4%) and use of rescue β_2 -agonists (0.12 puffs/day, 95% CI: 0–0.23) were less with the on-demand strategy compared with continuous treatment. In children, on-demand inhaled corticosteroid treatment compared with continuous treatment was associated with greater growth (0.41 cm, 95% CI: 0.13–0.69). However, the strength of evidence overall was considered low and the authors concluded that equivalence between the two strategies had not been established. A further systematic review of seven clinical trials including 1367 participants with asthma has been published recently [74]. The meta-analysis included a clinical trial in which the primary aim of the study was a comparison of physician-, biomarker- and symptom-based strategies for adjustment of inhaled corticosteroid therapy of patients with mild to moderate asthma receiving low-dose inhaled corticosteroids [75] (this study was excluded from the earlier review [67]). The meta-analysis found no significant difference in the rate of asthma exacerbations between continuous treatment compared with the on-demand strategy (0.96; 95% CI: 0.86–1.06) [74]. The continuous treatment group had a significant increase in asthma-free days and non-significant decreases in use of rescue β_2 -agonists and exhaled nitric oxide measurement compared with the on-demand strategy [74]. The conclusions from both systematic reviews and meta-analysis are similar. Overall, the improvement in efficacy outcomes including some measures of lung function, airway inflammation, asthma control and reliever use were greater with daily inhaled corticosteroid treatment compared with on-demand treatment, whereas in children modest growth suppression was associated with daily inhaled beclomethasone and budesonide [67]. The study design and main clinical outcomes of the clinical trials included in the systematic reviews [67,74] are included in TABLE 4 and are discussed below. Detailed analyses of the individual studies are available in the two systematic reviews [67,74].

Adults with asthma

The Improving Asthma Control Trial (IMPACT) was the first clinical study to compare on-demand versus continuous inhaled

Table 4. Summary of clinical trials assessing the efficacy and safety of on-demand vs daily inhaled corticosteroids in children and adults with persistent asthma.

Trial	Participants and intervention	Duration	Main clinical outcomes	Ref.
<i>Adults with asthma</i>				
IMPACT trial	225 corticosteroid-naïve adults with mild persistent asthma Randomized to on-demand inhaled budesonide, continuous inhaled budesonide (Turbuhaler®, 200 µg twice daily) or leukotriene-receptor antagonist (zafirlukast 20 mg twice daily) During exacerbations, all groups received budesonide 800 µg twice daily for 2 weeks Primary efficacy outcome: PEF	52 weeks	Morning PEF and time to the first exacerbation were similar in the on-demand and continuous inhaled budesonide treatment groups Continuous budesonide compared with other treatment strategies produced greater improvements in asthma control score, symptom-free days pre-bronchodilator FEV ₁ , bronchial hyperreactivity, sputum eosinophils and exhaled nitric oxide Clinical outcomes did not differ between on-demand inhaled budesonide and daily zafirlukast	[68]
BEST trial	466 adults with mild persistent asthma (70% corticosteroid naïve) Randomized to on-demand CFC-beclomethasone (250 µg) and albuterol in a single metered-dose inhaler, continuous inhaled beclomethasone (250 µg twice daily) plus albuterol as needed, 100 µg of albuterol as needed or continuous beclomethasone (250 µg) and albuterol in a single inhaler (twice daily) plus albuterol as needed During exacerbations, on-demand group received beclomethasone 250 µg and albuterol 100 µg in a single inhaler as required; continuous group received beclomethasone 250 µg twice daily + 'as-needed' albuterol 100 µg Primary efficacy outcome: morning PEF	24 weeks	Morning PEF and number of exacerbations were similar in the on-demand and continuous inhaled beclomethasone treatment groups, including with the continuous beclomethasone plus albuterol in a single inhaler group Clinical outcome were better in the on-demand inhaled beclomethasone plus albuterol group compared with the albuterol as-needed group Cumulative dose of inhaled beclomethasone was lower in the on-demand beclomethasone plus albuterol group (18.4 ± 25.2 mg) than in the group(s) receiving regular beclomethasone (76.9 ± 17.3 mg)	[69]
BASALT trial	342 adults with mild to moderate asthma controlled by low-dose inhaled corticosteroid therapy Randomized to three groups: assigned to physician assessment-based adjustment, biomarker-based (exhaled nitric oxide) and to symptom-based adjustment of inhaled corticosteroid dose All groups received beclomethasone (BDP-HFA Qvar®, 80 µg daily before randomization and the dose was adjusted every 6 weeks according to the adjustment strategy Primary outcome was time to treatment failure	36 weeks	There were no significant differences in time to treatment failure. The 9-month Kaplan–Meier failure rates were 22% (97.5% CI: 14–33%; 24 events) for physician assessment-based adjustment, 20% (97.5% CI: 13–30%; 21 events) for biomarker-based adjustment, and 15% (97.5% CI: 9–25%; 16 events) for symptom-based adjustment	[75]

BEST: Beclomethasone and salbutamol treatment; CFC: Chlorofluorocarbon; IMPACT: Improving Asthma Control Trial; MIST: Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers; PEF: Peak expiratory flow; SD: Standard deviation; TREXA: Treating Children to Prevent Exacerbations of Asthma.

Table 4. Summary of clinical trials assessing the efficacy and safety of on-demand vs daily inhaled corticosteroids in children and adults with persistent asthma (cont.).

Trial	Participants and intervention	Duration	Main clinical outcomes	Ref.
<i>School-age children with asthma</i>				
Helsinki Early Intervention trial	176 children aged 5–10 years with newly detected mild asthma Randomized to continuous inhaled budesonide Turbuhaler, (400 mg twice daily for 1 month, 200 mg twice daily for months 2–6, 100 mg twice daily for months 7–18), identical treatment to group 1 during months 1–6, then on-demand budesonide for exacerbations as needed for months 7–18, or disodium cromoglycate 10 mg three times daily for months 1–18. During exacerbations, budesonide 400 mg twice daily for 2 weeks Primary efficacy outcome: PEF	18 months	During months 7–18, continuous budesonide treatment compared with on-demand treatment resulted in fewer exacerbations (mean 0.97 vs 1.69), but similar PEF and number of asthma-free days Growth velocity was normalized during continuous low-dose budesonide and on-demand budesonide therapy and latter strategy was associated with catch-up growth Continuous budesonide treatment slowed down the increase in bone mineral density of the lumbar vertebrae, which was not seen in the on-demand group after the initial regular budesonide treatment Continuous inhaled budesonide compared with regular disodium cromoglycate in months 1–6 resulted in a improvement in lung function, fewer exacerbations and a small decline in growth velocity	[72,76]
TREXA trial	843 children and adolescents with mild persistent asthma aged 5–18 years Randomized to four groups: on-demand beclomethasone (BDP-HFA Qvar, 100 µg) with albuterol; continuous beclomethasone (100 µg daily) with beclomethasone plus albuterol as rescue; continuous beclomethasone (100 µg daily) with albuterol as rescue; albuterol as required During exacerbations: beclomethasone 100 µg for each two puffs of albuterol (200 µg) Primary outcome: time to first exacerbation that required oral corticosteroids	44 weeks	On-demand strategy and continuous strategies were better than placebo (49%, 95% CI: 37–61) for frequency of exacerbations (28%, 18–40 and 35%, 24–47, respectively) and frequency of treatment failure Linear growth was less in the continuous groups (1.1 cm (SD 0.3)) but not in the on-demand group compared with placebo	[73]
<i>Pre-school children with asthma</i>				
BEST for children trial	276 symptomatic children with frequent wheeze, aged 1–4 years Randomized to three groups: i) continuous beclomethasone nebulizer solution 400 µg daily plus 2500 µg albuterol as required, ii) on-demand beclomethasone 800 µg plus 1600 µg albuterol combination as required, iii) albuterol 2500 µg as required During exacerbations: treated as per GINA guidelines Primary efficacy outcome: percentage of symptom-free days	12 weeks	Compared with albuterol as required (61.0%, SD 24.8), the percentage of symptom-free days was higher with regular beclomethasone (69.6%, SD 20.8) but not significantly different from the on-demand group (64.9%, SD 24.7)	[70]
MIST trial	278 children aged 12 and 53 months with recurrent wheezing episodes, and at least one exacerbation in the previous year Randomized to two groups: on-demand budesonide inhalation suspension, 1 mg twice daily for 7 days, starting early during a predefined respiratory tract illness or continuous budesonide inhalation suspension, 0.5 mg nightly Primary efficacy outcome: frequency of exacerbations requiring oral glucocorticoid therapy	52 weeks	Frequency of exacerbations was similar between the two groups (rate per patient-year for continuous treatment 0.97 (95% CI: 0.76–1.22) vs on-demand strategy 0.95 (95% CI: 0.75–1.20) Mean exposure to budesonide was 104 mg less with the on-demand regimen than with the continuous regimen.	[71]

BEST: Beclomethasone and salbutamol treatment; CFC: Chlorofluorocarbon; IMPACT: Improving Asthma Control Trial; MIST: Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers; PEF: Peak expiratory flow; SD: Standard deviation; TREXA: Treating Children to Prevent Exacerbations of Asthma.

corticosteroid treatment in adults with mild persistent asthma (TABLE 4) [68]. The primary outcome was change in PEF in the intermittent strategy group compared with either inhaled budesonide (200 µg daily) or a leukotriene-receptor antagonist. There were no significant differences among the groups in morning PEF or the time to the first exacerbation of asthma. In the BEclomethasone and Salbutamol Treatment (BEST) study, adults with mild persistent asthma were randomized to either rescue use of beclomethasone (250 mg per puff) and albuterol in a single inhaler only when they had symptoms of asthma or to regular inhaled beclomethasone (250 mg per puff) daily [69]. The mean morning PEF was similar in the on-demand and regular treatment groups at the end of the study. The cumulative dose of inhaled beclomethasone was lower in the on-demand beclomethasone plus albuterol group than in the groups receiving regular beclomethasone. The Best Adjustment Strategy for Asthma in the Long Term (BASALT) trial found that among adults with mild to moderate persistent asthma controlled with low-dose inhaled corticosteroid treatment that the use of either biomarker-based or symptom-based adjustment of inhaled corticosteroids was similar to physician assessment-based adjustment [75].

Children with asthma

School-age children with asthma

In the Helsinki Early Intervention trial, school-age children with mild persistent asthma were randomized to three treatment strategies: on-demand inhaled budesonide, continuous inhaled budesonide 200 µg daily or regular disodium cromoglycate [72]. Regular use of budesonide resulted in better asthma control, whereas children treated with periodical inhaled budesonide did not show any slow-down in the increase in bone mineral density and standing height [76]. The long-term clinical relevance of this latter observation on the risk of fractures is uncertain. The Treating Children to Prevent Exacerbations of Asthma (TREXA) trial, also undertaken in school-age children with asthma, compared BDP-HFA Qvar 100 in treatment strategy groups with placebo over 44 weeks and found that the on-demand and continuous treatment with inhaled beclomethasone were more effective in reducing time to first exacerbation that required oral corticosteroids compared with placebo [73]. Continuous treatment was associated with a significant slow-down in growth, which was not found in the on-demand group. The authors suggested that the on-demand strategy may be an effective step-down strategy for children with well-controlled mild asthma.

Pre-school children with asthma

The BEST for children trial compared beclomethasone nebulizer solution administered in as dose of 400 µg daily with intermittent administration in a dose of 800 µg plus 1600 µg albuterol or albuterol 2500 µg as required [70]. Compared with albuterol as required, the percentage of symptom-free days was higher with regular beclomethasone, but not significantly different from the on-demand group. Overall, the continuous

strategy was the most effective treatment for frequent wheezing in pre-school children. The Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) trial undertaken in infants with asthma found that clinical efficacy outcomes with daily nebulized budesonide were similar to on-demand nebulized budesonide, but the continuous regime resulted in greater corticosteroid exposure at 1 year [71].

Commentary on clinical trials

While in the main the currently available data are reassuring, the choice of lung function as the primary outcome measure in several clinical trials in patients with mild persistent asthma may not be appropriate as this group of patients usually have normal lung function. Severe exacerbations occur in inhaled corticosteroid-naïve adult patients with mild persistent asthma at a rate of 0.77 per patient per year [2] but may be a more appropriate primary outcome to assess the safety and equivalence of on-demand versus continuous treatment regimens. Considerable expense will result from this choice due to clinical trials lasting for 2 years or longer being required. Many patients do not adhere to regular treatment with inhaled corticosteroids [45] and so the degree of non-adherence to continuous inhaled corticosteroid treatment is likely to remain an important issue and needs to be addressed. In addition, clinical trials in adults have excluded current smokers and the elderly and therefore the currently available results may not be relevant to a 'real-life' population of patients with mild persistent asthma and so future trials need to address these groups to ensure generalizability to 'real-life' clinical practice [60].

Place in management

Patients with mild asthma make up the majority of patients with asthma [1]. The goals of management in this group are to achieve excellent asthma control and to reduce the risks of exacerbations and long-term loss of lung function. The step-wise pharmacological approach to treatment of asthma is currently integrated into a management plan that includes non-pharmacological management approaches where appropriate, as well as regular assessment of current symptom control, risk of future exacerbations and adherence as well as inhaler technique [201,202]. These assessments are undertaken prior to a step-up or step-down in treatment. Continuous inhaled corticosteroid treatment is recommended at step 2 in both national and international guidelines for patients with mild persistent asthma [201,202]. However, guidelines do not currently provide recommendations on the intermittent use of inhaled corticosteroids.

Expert commentary

Clinical trials to date comparing on-demand with continuous inhaled corticosteroid in adults and children with asthma suggest that the efficacy of the on-demand strategy is similar in some clinical trials or less in other studies than continuous treatment whereas adverse effects in children may be greater with continuous treatment. Although it is uncertain whether issues around safety are relevant in mild persistent asthma

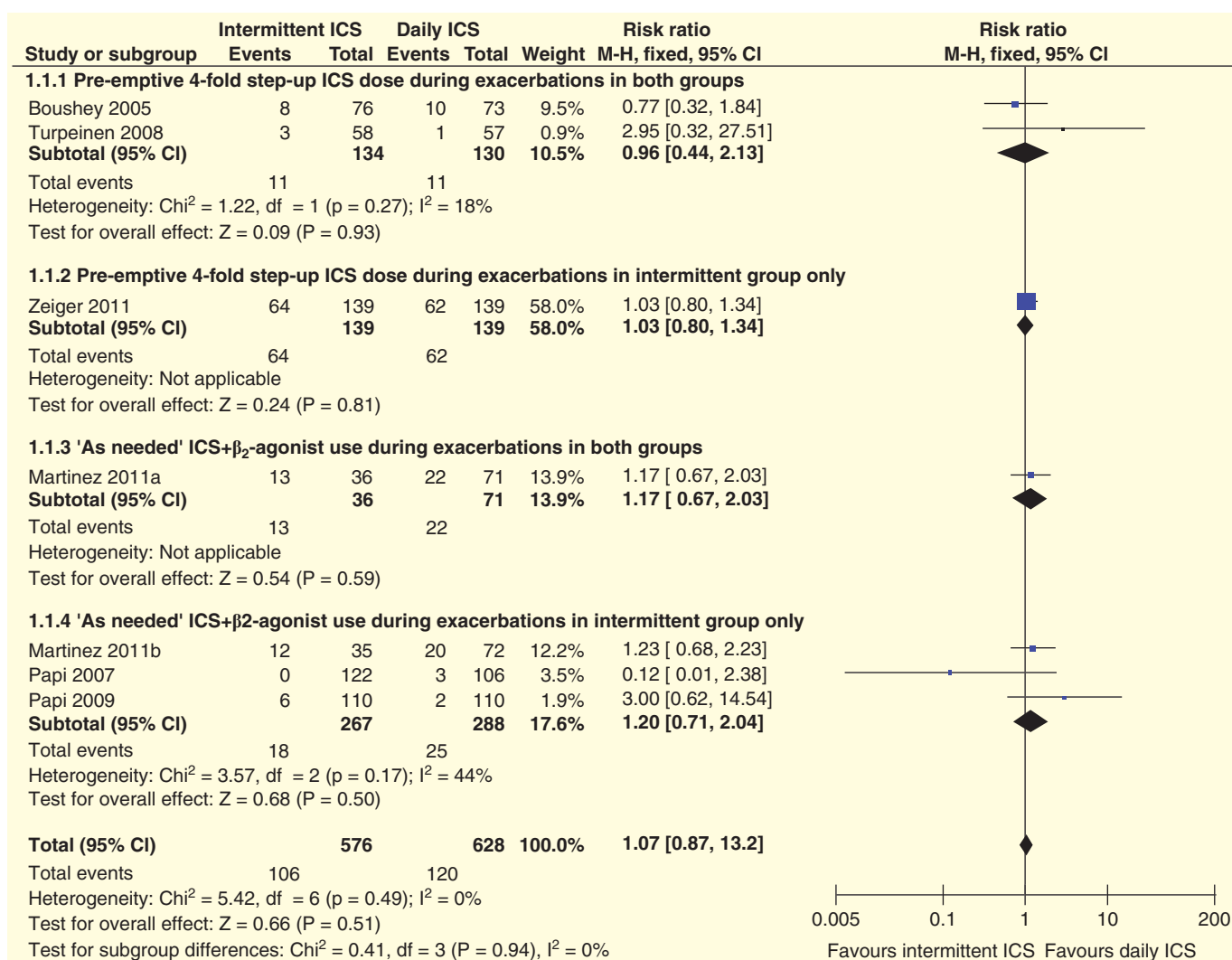


Figure 1. On-demand inhaled corticosteroid compared with continuous inhaled corticosteroid in patients with one or more exacerbations requiring oral corticosteroids (Forest plot).

ICS: Inhaled corticosteroids.

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where the total dose of inhaled corticosteroid administered are usually low. It should be noted that clinical trials to date have not assessed efficacy or safety on lung growth and lung function decline of the two strategies beyond 1 year. The on-demand strategy may be an effective step-down strategy for children and adults with well-controlled mild asthma on continuous treatment with inhaled corticosteroids however this still requires definitive examination in an appropriately designed clinical trial.

The inhaled corticosteroids used to date in clinical trials of continuous versus intermittent dosing strategies are budesonide and beclomethasone. Budesonide is deposited mainly in the large airways whereas HFA-BDP Qvar has greater lung deposition including the small airways. Small airway dysfunction, although more often associated with moderate to severe asthma, can occur in mild disease and is associated with worse

control [26–31,77]. It has been suggested that patients with mild persistent asthma in whom forced expiratory volume in 1 s is normal, but who exhibit small airways dysfunction on lung function testing may be suitable candidates for extrafine-particle HFA formulations of inhaled corticosteroid either alone or in combination with long-acting β_2 -agonist [78], although this hypothesis is still to be tested. However, in this group it may be preferable to use a continuous higher-dose regimen to maximize treatment with inhaled corticosteroids to the small airways [27,78]. To date, clinical trials have not been undertaken to establish the effectiveness of this strategy.

Leukotriene antagonists are another treatment option in patients with mild persistent asthma although less effective than continuous low-dose inhaled corticosteroids [201]. In a pragmatic 'real-life' trial in primary care in the UK, at 2 months a leukotriene receptor antagonist was as effective as an inhaled

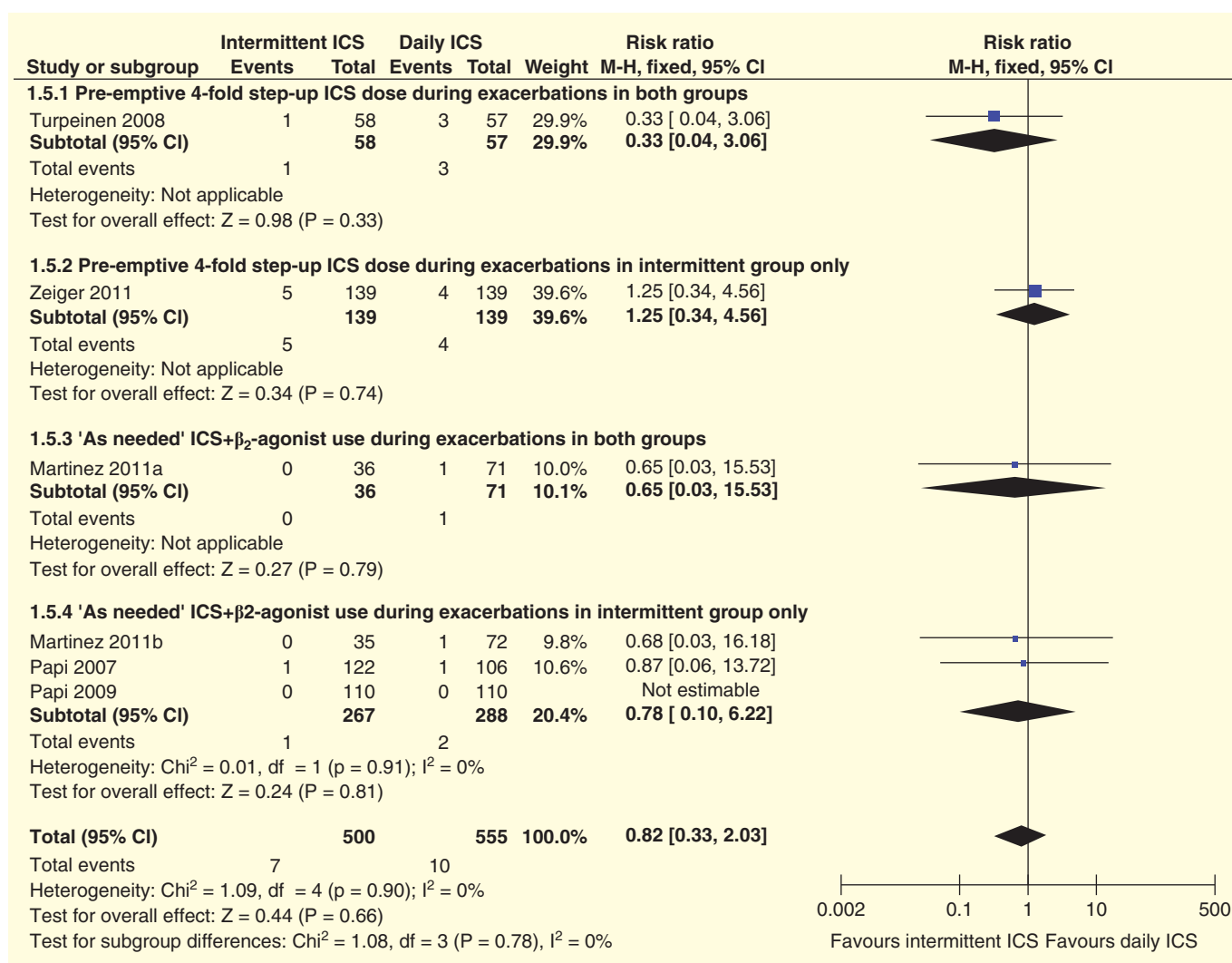


Figure 2. On-demand inhaled corticosteroid compared with continuous inhaled corticosteroid in patients with serious adverse events (Forest plot).

ICS: Inhaled corticosteroids.

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corticosteroid at Step 2 [79], possibly due to the recruitment of patients such as the elderly, the obese or cigarette smokers [80], who are often excluded from clinical trials and may gain greater benefit. A randomized, parallel-group 6-month study that evaluated the efficacy of oral montelukast, fluticasone propionate and placebo in 1019 patients with chronic asthma who smoke, reported that both interventions produced similar, but small, improvements in the percentage of asthma-control days [81]. Patients with a light smoking history showed more benefit with inhaled fluticasone, whereas those with a heavy smoking history showed more benefit with montelukast [81]. Although further studies are required to confirm these findings, they highlight the importance of recruiting 'real-life' participants to clinical trials in asthma. In the IMPACT trial, clinical outcomes did not differ between on-demand inhaled budesonide and daily zafirlukast [68]. It is currently unclear if the effectiveness of on-

demand inhaled corticosteroids is equivalent to treatment with leukotriene receptor antagonist therapy in a 'real-life' asthmatic population.

Patient preference is an important factor in deciding the most appropriate treatment options. Some patients may prefer the on-demand inhaled corticosteroid strategy and to step-up treatment at the time of increased symptoms. The effectiveness of maintenance and relief strategies at Step 3 with either the SMART (Single inhaler Maintenance And Reliever Therapy) regimen [82], which involves using both budesonide and formoterol in a single inhaler, or the MART (Maintenance And Relief Therapy) regimen [83], which involves using inhaled extrafine-particle size beclomethasone and formoterol in single inhaler demonstrates the ability of patients to auto-titrate symptoms to drug use. These trials support the concept of patients using inhaled

corticosteroids on an as-required basis in milder disease. Clinicians need to discuss with patients the potential risks and benefits of each inhaled corticosteroid treatment strategy. Regular follow-up of patients with mild asthma is important to ensure that whichever strategy is chosen results in well-controlled asthma.

Five-year view

There is a need for large long-term studies in adults with asthma and school-age and pre-school age children with asthma that compare on-demand and continuous inhaled corticosteroid strategies, to establish whether each option is equivalent in efficacy and safety. For example, it will be important to determine that the on-demand strategy does not result in loss of lung function over time or that the continuous strategy does not result in impaired growth in children.

Several once-daily inhaled corticosteroids used alone or in combination with inhaled ultra long-acting β_2 -agonists are under development, but are not yet licensed for use. Adherence may be improved by once-daily administration of these products. Non-steroidal selective glucocorticoid receptor modulators are also in development with the aim of improving the therapeutic ratio of corticosteroids by dissociating transactivation, which is associated with the adverse effects of corticosteroids, from the beneficial effect of transrepression [9,84]. It will be important to establish the effectiveness of these drugs in comparison with on-

demand inhaled corticosteroid treatment in mild persistent asthma.

With the development of a personalized approach to the treatment of asthma will it be possible in the future to identify subgroups of patients using physiological, inflammatory and/or genetic biomarkers that can predict those patients who are suited for continuous or the on-demand treatment option? For example, if a patient with asthma is at increased risk of accelerated loss of lung function or has small airway dysfunction then continuous treatment may be a more appropriate option.

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Key issues

- Based on the observations that the benefits of regular inhaled corticosteroids on lung function are not lost if treatment is delayed and that many patients do not adhere to continuous treatment with inhaled corticosteroids, but rather take them intermittently, it has been proposed that inhaled corticosteroids should be used on-demand, when asthma symptoms are troublesome, rather than on a continuous basis.
- The inhaled corticosteroids used to date in clinical trials of continuous versus intermittent dosing strategies are budesonide and beclomethasone. Budesonide is deposited mainly in the large airways whereas extrafine-particle inhaled beclomethasone have greater lung deposition including the small airways. It has not been clearly demonstrated that equipotent doses of small-particle inhaled corticosteroids compared with large-particle inhaled corticosteroids either improve efficacy or reduce systemic adverse effects.
- Clinical trials to date comparing on-demand with continuous inhaled corticosteroid in adults and children with asthma suggest that the efficacy of the on-demand strategy is similar or less than continuous treatment whereas adverse effects in children may be greater with continuous treatment although it is uncertain whether this is relevant in mild persistent asthma where the total dose of inhaled corticosteroid administered are usually low.
- Patient preference is an important factor in deciding the most appropriate treatment options. Many patients do not adhere to regular treatment with inhaled corticosteroids and may prefer the on-demand inhaled corticosteroid strategy and to step-up treatment at the time of increased symptoms.
- There is a need for large long-term studies in adults with asthma and in school-age and pre-school age children with asthma that compare the on-demand and continuous inhaled corticosteroid strategies to establish whether the options are equivalent in efficacy and safety.
- With the development of a personalized approach to the treatment of asthma, future research will need to determine whether subgroups of patients can be identified by physiological, inflammatory and or genetic biomarkers that can predict those patients who are suited for continuous therapy or the on-demand option.

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