Place in therapy review

Ciclesonide in persistent asthma: the evidence of its therapeutic value

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Abstract

Introduction: Asthma, a respiratory disease associated with airway inflammation and hyperresponsiveness, is one of the most prevalent chronic diseases worldwide affecting both children and adults. Inhaled corticosteroids are considered to be the cornerstone of asthma management. Ciclesonide, an airway-activated inhaled corticosteroid, has been developed for the management of persistent asthma. Its once-daily administration and airway activation may be advantageous in the treatment of asthma.

Aims: The purpose of this article is to review the place in therapy of ciclesonide in the management of patients with persistent asthma based on the available clinical evidence.

Evidence review: The available evidence indicates that ciclesonide has an effect on pulmonary function (forced expiratory volume in 1 s, forced vital capacity, and peak expiratory flow), as well as producing improvements in patient-reported symptoms that are equivalent to those achieved with other inhaled corticosteroids. A few studies have focused on health-related quality of life and have demonstrated a positive effect with ciclesonide treatment. Its pharmacokinetic profile may offer advantages in terms of adverse effects, both local and systemic, although most of the data come from 12-week studies.

Place in therapy: The current evidence shows that ciclesonide offers another alternative among inhaled corticosteroids, with the potential for fewer adverse effects. The unique pharmacokinetic profile of ciclesonide allows once-daily administration and the airway activation of the drug appears to confer clinical benefit in the treatment of asthma. Its lack of systemic adverse effects make it a viable option for pediatric use.

Key words: antiinflammatory, asthma, ciclesonide, evidence, inhaled corticosteroids, outcomes

Core evidence place in therapy summary for ciclesonide in persistent asthma

Outcome measure	Evidence	Implications
Patient-oriented evidence		
Improvement in asthma symptoms	Clear	Effects are similar to other inhaled corticosteroids
Reduction in rescue medication	Clear	Effects are similar to other inhaled corticosteroids
Improvement in quality of life	Substantial	Beneficial effects on patient-perceived quality of life
Reduction in oral corticosteroid use	Moderate	Reduction in the regular use of oral corticosteroids likely to decrease the incidence of adverse systemic effects
Disease-oriented evidence		
Preservation of hypothalamic–pituitary–adrenal axis	Substantial	Lack of effect on hypothalamic–pituitary–adrenal axis for up to 1 year; suitable for use in pediatric patients
Lower incidence of local adverse effects	Clear	Fewer local adverse effects (e.g. oropharyngeal effects) compared with other inhaled corticosteroids
Improvement in lung function (FEV_1, FVC, PEF)	Clear	Ciclesonide as effective as budesonide and fluticasone, at least in the short term
Economic evidence		
Cost effectiveness as an inhaled corticosteroid in persistent asthma in adults and children	No evidence	Evidence required

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

Scope, aims, and objectives

Ciclesonide (Alvesco®, ALTANA Pharma AG), an airway-activated inhaled corticosteroid, has been developed for the management of persistent asthma. Its once-daily administration and airway activation may be advantageous in the treatment of asthma. Pharmacologically, the activation of ciclesonide to its active metabolite, desisobutyryl-ciclesonide (des-CIC), by airway esterases is novel. This local activation of drug provides concentrated activity of ciclesonide at the target organ, the lungs, and may decrease the potential for local and systemic adverse effects. Data from phase III clinical trials evaluating ciclesonide in the management of adult and pediatric patients with persistent asthma are available.

The purpose of this article is to review the place in therapy of ciclesonide in the management of patients with persistent asthma based on the available clinical evidence.

Methods

The English language medical literature was reviewed for appropriate articles relating to ciclesonide for the treatment of asthma. The following databases were searched during August 2005 using the search terms "ciclesonide," "El 876," "By 90107," and "Alvesco":

- PubMed, http://www.ncbi.nlm.nih.gov
- EMBASE, http://www.datastarweb.com
- BIOSIS, http://www.datastarweb.com
- York University Centre for Reviews and Dissemination (CRD) databases, http://www.york.ac.uk/inst/crd/crddatabases.htm
- National Guideline Clearinghouse, http://www.guideline.gov
- Clinical trial registries, http://www.clinicaltrials.gov, http://www.clinicalstudyresults.org
- National Coordinating Centre for Health Technology Assessment (NCCHTA), http://www.ncchta.org
- Cochrane Database of Systematic Reviews (CDSR), http://www.cochrane.org/index0.htm
- National Institute for Health and Clinical Evidence (NICE), http://www.nice.org.uk
- Clinical Evidence (BMJ), http://www.clinicalevidence.com

No date limitations were placed on the search and only studies in patients with asthma were included. Abstracts from the American Thoracic Society (ATS) (http://www.thoracic.org) and the European Respiratory Society (ERS) meetings (http://www.ersnet.org/ers) for 2002–2005 were also reviewed using the same search terms to identify studies that have not yet been published in full.

Numerous guidelines related to asthma management were identified, but only two recent guidelines applicable on a global level were considered relevant for this review. No studies were identified from a review of clinical trials databases. A single Health Technology Assessment of ciclesonide was identified from the York University Centre.

The levels of evidence identified from the literature searches are summarized in Table 1. Twenty full papers were identified in the initial search. Records were manually reviewed and 12 papers were excluded: pharmacokinetic (n=5), *in vitro* (n=1), animal studies (n=2), study other than a large, controlled clinical trial (n=3), or citations that mentioned ciclesonide but did not investigate its clinical use (n=1). Sixty-one abstracts were also reviewed manually. Exclusions included: published in full (n=4), pharmacokinetic (n=5), animal studies (n=6), *in vitro* (n=10), study other than a large, controlled clinical trial (n=11), and presentation of study results at more than one professional meeting (n=6).

The search was updated on February 7 and on June 30, 2006 and 22 new records were identified from the previous search. Eleven records were excluded as they were nonsystematic reviews (n=6), editorials (n=1), *in vitro* (n=2), small pharmacokinetic study (n=1), or an indication other than asthma (n=1). A systematic review (Dyer et al. 2006) was not included in the evidence base, as it was limited to small phase II studies comparing ciclesonide with other inhaled corticosteroids, rather than more recent larger phase III randomized controlled trials (RCTs).

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	20	61
records excluded	12	42
records included	8	19
Additional studies identified[a]	3	3
Search update, new records	22	22
records excluded	12	18
records included	10	4
Level 1 clinical evidence	2	0
Level 2 clinical evidence	18	27[b]
Level ≥3 clinical evidence	1	0
trials other than RCT	1	
case reports		
Economic evidence	0	0
Total records included	21	27

[a]Additional studies identified = any relevant study that was picked up from a source other than the main searches, e.g. a reference list.
[b]Includes several subanalyses from six RCTs.
For definitions of levels of evidence see Editorial Information on inside back cover.
RCT, randomized controlled trial.

In addition, a further level 3 pharmacokinetic study was identified and included (Nave et al. 2006), along with 22 abstracts of meeting presentations, of which 4 were included following removal of duplicates.

Disease overview

Asthma, a chronic respiratory disease of both children and adults, is one of the most prevalent chronic diseases in the world affecting approximately 300 million people (Bousquet et al. 2005; Masoli et al. 2005). An estimated 250 000 deaths caused by asthma occur annually; one in every 250 deaths worldwide is thought to be secondary to asthma (Bousquet et al. 2005; Masoli et al. 2005).

The impact of asthma is far-reaching in both the adult and pediatric population and includes an effect on activities of daily living that extends to participation in school, work, and family life. Globally, about 15 million disability-adjusted life years (DALYs) are lost annually due to asthma, a number similar to that associated with diabetes, cirrhosis, or schizophrenia (Masoli et al. 2005). Direct medical costs related to medications and hospital admissions, and indirect medical costs related to loss of work and premature mortality are significant. Direct medical costs of asthma treatment account for up to 3% of total medical expenditures for many countries (Bousquet et al. 2005).

Although the exact etiology of asthma remains poorly understood it is thought to have both genetic and environmental causes and is considered a chronic inflammatory disease. Asthma is characterized by bronchial hyperreactivity caused by chronic inflammation of the airways. Bronchial hyperreactivity is associated with reversible airflow obstruction and episodes of wheezing, breathlessness, chest tightness, and coughing (especially in the early morning or at night). There is no cure for asthma and the goal of treatment is to achieve and maintain control of symptoms, prevent exacerbations, reduce/eliminate side effects from medications, and allow patients to have an optimal quality of life. The potential for development of adverse effects associated with asthma treatment has been noted to impact patient adherence to therapy (Goeman 2002).

Current therapy options

Over the past two decades the treatment of asthma has received increased attention and guidelines for the management of asthma have been published [Global Initiative for Asthma (GINA) strategy, World Health Organization (WHO)/National Heart, Lung, and Blood Institute (NHLBI); Anon. 2005b). A global strategy for asthma management and prevention—the result of a collaborative effort of GINA, WHO, and the NHLBI—was first issued in 1995. Updates to this guideline have been released with the most recent being in 2004. Asthma management protocols and guidelines focus on the inflammatory component of the disease and recommend a stepped-care approach to disease management (Table 2).

Many pharmacologic entities are available for the chronic management of persistent asthma, but inhaled corticosteroids are the cornerstone of therapy. Corticosteroids can be administered either orally or via inhalation, although the adverse effect profile significantly favors the latter. Inhaled corticosteroids are considered the most effective therapy for persistent asthma and are the preferred treatment for all patients with persistent disease symptoms (Anon. 2005b).

All of the available inhaled corticosteroids produce their effects by interacting with intracellular glucocorticoid receptors, which are present throughout the body. In the treatment of asthma, the effect of these agents on pulmonary glucocorticoid receptors produce the desired effects but interaction with glucocorticoid receptors outside the lungs can lead to unwanted adverse effects such as suppression of the hypothalamic–pituitary–adrenal axis (HPA), reduction of bone density, and growth suppression. Beneficial pharmacologic effects of these agents include decreasing inflammatory cells in the airway and increasing the release of antiinflammatory cytokines (Hübner et al. 2005). The decrease in inflammatory mediators results in a reduction of airway inflammation and hyperreactivity, improved pulmonary function, symptom control, and reduction of exacerbations (Kelly 2003).

The principal goal of inhaled corticosteroid therapy is to have a high level of antiinflammatory effect with minimal adverse effects (Kelly 2003). Although differences in pharmacokinetic parameters and potency exist, the currently available agents (Table 3) are considered equally efficacious when administered at equipotent doses (O'Connell 2005). The ideal inhaled corticosteroid for patients with asthma has a high degree of lung deposition with a low level of systemic bioavailability providing therapeutic benefit (high glucocorticoid receptor affinity) without significant adverse effects. Systemic exposure can be minimized by high protein binding and a rapid clearance rate (Berger 2005). Use of a prodrug that is not pharmacologically active until it undergoes a metabolic transformation has been shown to decrease oropharyngeal effects and might result in improved pulmonary targeting (Hübner et al. 2005).

Smaller particle size, physical properties of the compounds, delivery device used, and inhaler technique all have an impact on the rate of lung deposition (Hübner et al. 2005). Higher rates of lung deposition translate to an increased amount of drug available at the intended site of action (lungs) and a lower amount available for oral absorption and systemic availability, and hence fewer adverse effects. In addition, lipid conjugation of the compound can provide a reservoir in the lungs allowing for a slow release of active compound (Berger 2005).

Of particular concern for long-term treatment of persistent asthma is an agent's propensity to cause systemic side effects. Systemic exposure to an inhaled corticosteroid is tied to its potential for adverse effects. There is little concern about systemic effects with the use of low-dose inhaled corticosteroids (doses of $\leq$500 mcg budesonide or equivalent) (Anon. 2005b). However, at high doses concern remains that these medications may cause HPA axis suppression, decreased bone mineralization, cataracts, glaucoma, and a reduction in the rate of bone growth in children. It is important to note that while HPA axis suppression

Table 2 | Pharmacologic management of asthma: stepped approach (adapted from Anon. 2005b)

Category of asthma	Characteristics	Daily medication[a]
Adults and children >5 years		
Intermittent	• Symptoms <once/week • Brief exacerbations • Nocturnal symptoms ≤2 nights/month • FEV_1 or PEF ≥80% predicted • PEF or FEV_1 variability <20%	• None
Mild persistent	• Symptoms >once/week, but <once/day • Exacerbations may affect activity and sleep • Nocturnal symptoms >2 nights/month • FEV_1 or PEF ≥80% predicted • PEF or FEV_1 variability 20–30%	• Low-dose inhaled corticosteroid • Alternative: cromolyn, leukotriene modifier, nedocromil, or sustained-release theophylline
Moderate persistent	• Daily symptoms • Exacerbations may affect activity and sleep • Nocturnal symptoms >once/week • Daily use of short-acting inhaled $beta_2$ agonist • FEV_1 or PEF 60–80% predicted • PEF or FEV_1 variability >30%	• Low to medium-dose inhaled corticosteroid and long-acting inhaled $beta_2$ agonist • Alternative: – Increase inhaled corticosteroid within medium dose range or – Low to medium-dose inhaled corticosteroid and either leukotriene modifier or theophylline
Severe persistent	• Continuous symptoms • Frequent exacerbations • Frequent nocturnal symptoms • Limitation of physical activities • FEV_1 or PEF 60% predicted • PEF or FEV_1 variability >30%	• High-dose inhaled corticosteroid and long-acting inhaled $beta_2$ agonist • If needed: oral corticosteroid, sustained-release theophylline, leukotriene modifier, antiimmunoglobulin E antibody (adults and children ≥2 years)
Infants and young children <5 years		
Mild intermittent[b]	• Symptoms <once/week • Brief exacerbations • Nocturnal symptoms <2 nights/month • FEV_1 or PEF ≥80% predicted • PEF or FEV_1 variability <20%	• None
Mild persistent	• Symptoms >once/week, but <once/day • Exacerbations may affect activity • Nocturnal symptoms >2 nights/month • FEV_1 or PEF ≥80% predicted • PEF or FEV_1 variability 20–30%	• Low-dose inhaled corticosteroid • Alternative: cromolyn, leukotriene modifier, nedocromil, or sustained-release theophylline
Moderate persistent	• Daily symptoms • Exacerbations affect activity • Nocturnal symptoms >once/week • FEV_1 or PEF 60–80% predicted • PEF or FEV_1 variability >30%	• Low-dose inhaled corticosteroid and long-acting inhaled $beta_2$ agonist (if needed medium dose can be used) or • Medium-dose inhaled corticosteroid • Alternative: low-dose inhaled corticosteroid (if needed medium dose can be used) and leukotriene modifier or theophylline
Severe persistent	• Continuous symptoms • Frequent nocturnal symptoms • Limitation of physical activity • FEV_1 or PEF ≤60% predicted • PEF or FEV_1 variability >30%	• High-dose inhaled corticosteroid and long-acting inhaled $beta_2$ agonist • If needed: oral corticosteroid

[a]A short-acting inhaled $beta_2$ agonist should be used as needed to relieve acute symptoms; use should be limited to no more than 3–4 times/day.
[b]Children with intermittent asthma but severe exacerbations should be managed as having moderate persistent asthma.
FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow.

Table 3 | Pharmacokinetic profiles of currently available inhaled corticosteroids (Reynolds & Scott 2004; Anon. 2005a; Hübner et al. 2005; Wickersham & Novak 2005)

Drug	Lung deposition (MDI-HFA) (%)	Oral bioavailability[a] (%)	Protein binding (%)	Metabolism	Excretion	Suggested dosing frequency
Beclomethasone propionate	51[b]	26	87	Hepatic	Feces, urine (<10%)	Twice daily
Budesonide	28	11–32	88	Hepatic	Urine (60%), feces	Once or twice daily[a]
Ciclesonide	52	<1	99	Hepatic	Feces (77.9%)	Once daily
Flunisolide	39	7	80	Hepatic	Renal (50%), feces (40%)	Twice daily
Fluticasone propionate	16	<1	90	Hepatic	Feces (urine <0.02%)	Twice daily
Mometasone furoate	–	11	98–99	Hepatic	Feces (74%), urine (8%)	Once or twice daily
Triamcinolone acetonide	22[b]	21.5	71	Mostly hepatic, some renal	Urine (40%), feces (60%)	Twice daily

[a]Depends on the delivery device used.
[b]Delivery device not specified.
MDI-HFA, metered-dose inhaler with hydrofluoroalkane propellant.

and decreased osteoblast activity have been reported with high-dose inhaled corticosteroid therapy, the clinical significance of these effects is controversial. Additionally, patients receiving high doses of inhaled corticosteroids may be exposed to intermittent courses of systemic glucocorticoids that complicate the assessment of the impact of high-dose inhaled corticosteroid treatment alone (Anon. 2005b). Of the available inhaled corticosteroids, comparative studies have shown that budesonide, mometasone, and fluticasone have a lower potential to cause systemic effects as compared with beclomethasone dipropionate and triamcinolone (Crim et al. 2001; Anon. 2005b).

Ideally, once a patient's symptoms are controlled, the dose of inhaled corticosteroid should be reduced to the minimum effective dose to promote safe and cost-effective asthma control (British Thoracic Society 2005). Unfortunately, this approach is not always undertaken and patients are not infrequently exposed to unnecessarily high doses and an increased risk of adverse effects (O'Connell 2005).

Beyond the specific drug selected, the device used to deliver the therapeutic entity can have a profound effect on treatment outcome. In an attempt to maximize drug delivery to the lungs, a variety of inhaler devices have been developed. The device also impacts the efficacy of therapy and has associated advantages and disadvantages (Table 4). The delivery device as well as the specific drug evaluated and the dose selected must all be considered when evidence of inhaled corticosteroid efficacy and adverse effects are taken into account. Environmental concerns have mandated alternatives to the use of chlorofluorocarbon (CFC) propellants in metered-dose inhalers. The change to hydrofluoroalkane propellants has resulted in some products that have different characteristics from previous formulations (Dolovich et al. 2005). Therefore, interpretation of reported efficacy and adverse effect data also requires an understanding of the propellant used.

Even at low daily doses, local adverse effects (dysphonia, oral candidiasis, and pharyngitis) to inhaled corticosteroids are reported at widely varying rates (5–58%) (Roland et al. 2004). The reported prevalence of these local effects is influenced by the type of study, length of observation, delivery device used, and method for recording (questionnaire or clinical examination). Local adverse effects may complicate treatment and lead to a disruption of therapy and worsening of disease.

Despite advances in delivery device and drug development, there is still a need for inhaled corticosteroid therapies that are highly specific to the site of action, the lungs, with minimal systemic absorption. Ciclesonide was developed in response to this need.

Clinical evidence with ciclesonide in asthma

Level 2 evidence from fully published studies investigating the efficacy and safety of ciclesonide is available, including placebo-controlled studies (Chapman et al. 2005; Langdon et al. 2005; Pearlman et al. 2005; Bateman et al. 2006b; Gelfand et al. 2006) and trials with active comparator (Buhl et al. 2005a; Niphadkar et al. 2005; Boulet et al. 2006a; Hansel et al. 2006). Further evidence is also currently available in abstract form only, hindering full critical appraisal. Outcomes studied include disease-oriented measurable endpoints of respiratory function, inflammatory markers, and HPA suppression, as well as patient-oriented outcomes such as asthma symptoms, health-related quality of life (HRQOL), and use of rescue medication. Comparator drug propellant is not consistently reported which makes an assessment of delivery device difficult.

Ciclesonide is a prodrug whereas the other inhaled corticosteroids are delivered to the site of action in their active form. Ciclesonide is converted to its active and highly potent metabolite, des-CIC, by esterases in the airways, thus providing active drug at the intended site of action. Ciclesonide is also

Table 4 | Advantages and disadvantages of portable delivery devices for inhaled corticosteroids (Dolovich et al. 2005)

Device	Advantages	Disadvantages
Pressurized metered-dose inhaler	No contamination Dose–dose reproducibility Some can be used with breath-actuated mouthpiece	Requires coordination and good technique High pharyngeal deposition Difficult to determine remaining dosage
Holding chamber, spacers	Decreased need for patient coordination Decreased pharyngeal deposition	Added expense Less portable than metered-dose inhaler alone Dose delivered might be reduced
Dry-powder inhalers	Less patient coordination required: breath actuated No propellant required Dose counters in most newer dosage forms	Can deliver high pharyngeal deposition Moderate to high inspiratory flow required for actuation

formulated in solution which in comparison with suspensions is likely to improve lung deposition characteristics (Berger 2005). In addition, other properties of ciclesonide and des-CIC, including low oral bioavailability (<1%), rapid systemic clearance and a high degree of plasma protein binding (99%) are designed to reduce the potential for systemic side effects.

Therefore, the pharmacologic and pharmacokinetic characteristics of ciclesonide are intended to provide advancements in the treatment of asthma with a potentially improved safety profile.

Systemic absorption

In human lung tissue, a reversible lipid conjugation of des-CIC has been demonstrated. This may account for the prolonged antiinflammatory activity of inhaled ciclesonide in the lungs as this conjugated des-CIC may act as a reservoir (Berger 2005).

The small particle size of ciclesonide improves its pulmonary deposition; studies have shown that up to 52% of an inhaled dose of ciclesonide is deposited in the small airways and alveoli following administration, and that the amount of deposition is not influenced by the use of a spacer device (Drollmann et al. 2006; Newman et al. 2006). The pharmacokinetics of ciclesonide and des-CIC are similar in healthy subjects and in patients with asthma, confirming that airway activation of the drug is unimpaired by the disease (Nave et al. 2006).

Compared with fluticasone and budesonide, smaller amounts of ciclesonide are available for systemic absorption through the gastrointestinal tract as lower amounts are deposited in the mouth and oropharynx. In a study of adults with bronchial asthma, the oropharyngeal deposition of ciclesonide was about 50% of that reported with fluticasone propionate, with 90% less des-CIC present in the oropharyngeal cavity compared with fluticasone following inhalation (Richter et al. 2005). Following administration of ciclesonide and budesonide to healthy volunteers, the maximal concentrations of ciclesonide and des-CIC recovered from oropharyngeal wash were 30% and 0.67% of budesonide, respectively (Nave et al. 2005a). Ciclesonide and budesonide concentrations in the wash decreased rapidly within 15 min of administration. The concentrations of des-CIC in the oropharynx 60 min after inhalation were only 4% of the budesonide concentration (Nave et al. 2005a), and 8% of the fluticasone concentration (Richter et al. 2005).

Ciclesonide undergoes first-pass hepatic inactivation (>99%) following oral administration, rendering systemic bioavailability from the oral route essentially negligible (Nave et al. 2004). Furthermore, there is a low potential for adverse systemic side effects with inhaled ciclesonide as it is highly protein bound (>99%) and a low fraction of unbound active metabolite is available in the systemic circulation (Rohatagi et al. 2005). The unbound fraction is also rapidly cleared further limiting systemic availability (Berger 2005).

Pulmonary function

Laboratory measures of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and peak expiratory flow (PEF) provide a direct, objective measure of treatment effect on airflow limitation in asthma. Use of a spirometer to assess FEV_1 and FVC is helpful for diagnosing and monitoring the progress of asthma and response to therapy. Measurement of PEF with a peak expiratory flow meter can provide additional asthma monitoring information. However, PEF measures are not interchangeable with FEV_1 and FVC, and do not always correlate with asthma severity; the relationship between FEV_1 and PEF and asthma severity, airway inflammation, and HRQOL is complex and not well established.

Initial phase II studies documented a decrease in airway hyperresponsiveness after adenosine monophosphate (AMP) challenges with ciclesonide therapy; efficacy was similar to that of both fluticasone and budesonide (Taylor et al. 1999; Kanniess et al. 2001; Lee et al. 2004; Derom et al. 2005).

In placebo-controlled trials, ciclesonide demonstrated improvements in pulmonary function over a range of doses in patients with asthma with varying degrees of severity from mild to severe (Table 5). Single daily ciclesonide doses of at least 80 mcg daily were associated with significant improvements from baseline in pulmonary function compared with placebo (Langdon et al. 2005). Studies comparing single daily ciclesonide doses of 800 and 1600 mcg have not demonstrated superiority of the higher dose regimen (Chapman et al. 2002; O'Connor et al.

Table 5 | Effect of ciclesonide on lung function in patients with moderate to severe asthma (level 2 evidence; all trials randomized, double-blind, parallel-group, placebo-controlled, 12 weeks' duration)

Treatment (mcg)	n	Baseline FEV_1 (% of predicted)	Outcome				Reference
			FEV_1 (mL)	FEV_1 (%) change from baseline	FVC (mL)	Morning PEF (L/min)	
CIC 160 qd CIC 640 qd Placebo	107 112 110	60–90	Maintained with both doses[a] –144	NR	+59 +9 –161	Stable for both doses (P<0.0001) –29	Chapman et al. 2005
CIC 80 qd CIC 320 qd Placebo	120 115 125	60–95	+130 (P=0.0044)[b] +190 (P=0.0001)[b] –30	NR	+190 (P=0.0203)[b] +200 (P=0.0197)[b] +40	+2[c] (P=0.0012)[b] +3[c] (P=0.0006)[b] –18	Langdon et al. 2005
CIC 80 qd CIC 160 qd CIC 320 qd Placebo	257 250 255 249	60–85	+280 (P≤0.0007)[b] +290 (P≤0.0007)[b] +310 (P≤0.0007)[b] +170	NR	NR	10.93[c] (P=0.0003)[b] 21.06[c] (P<0.0001)[b] 17.22[c] (P<0.0001)[b] –1.70[c]	Pearlman et al. 2005
CIC 320 bid[d] CIC 640 bid[d] Placebo[d]	47 49 45	40–80	Trend toward higher values[e] NR	NR NR NR	NR NR NR	+4.32[b,c] +15.97[b,c] –0.7[b,c]	Bateman et al. 2006b

All P values vs placebo.

[a]P=0.007 for CIC 160 and P=0.0108 for CIC 640.

[b]Reported as a mean value.

[c]PEF change from baseline to week 12.

[d]Patients also received oral prednisone 5–30 mg/day and/or 10–60 mg on alternate days.

[e]P=0.0237 CIC 320 bid vs placebo, P=0.0277 CIC 640 bid vs placebo.

+, increase over study period; –, decrease over study period; bid, twice daily; CIC, ciclesonide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NR, not reported; NS, not significant; PEF, peak expiratory flow; qd, once daily.

2002). More recent data, however, show that compared with ciclesonide 160 mcg once daily, ciclesonide 320 mcg twice daily resulted in significantly improved PEF (P=0.0014) in 680 patients with severe asthma (Bateman et al. 2006a). A dose–response effect was also demonstrated in a 3-week study investigating ciclesonide 40, 80, 160, and 320 mcg on exercise-induced bronchoconstriction in 26 patients with mild asthma (Subbarao et al. 2006). Daily dosing given either in the morning or in the evening is associated with positive treatment response (Postma et al. 2001).

Ciclesonide 80 mcg has also been shown to block allergen-induced lung function responses and measures of airway inflammation in patients with mild atopic asthma (Gauvreau et al. 2005). In this randomized three-way crossover study 21 patients were treated with ciclesonide 40 or 80 mcg or placebo for 7 days and challenged with inhaled allergen. Compared with placebo, ciclesonide 80 mcg/day attenuated the allergen-induced airway response (P<0.025), the sustained fall in FEV_1 measures 24 hours postchallenge (P<0.025), and the allergen-induced accumulation of eosinophils into the airways (P<0.025). Similarly, after 4 weeks of treatment with ciclesonide 160 mcg once daily, inflammatory response as assessed by AMP bronchial challenge, exhaled nitric oxide, and sputum eosinophil count was significantly reduced in 17 patients with asthma (Wilson et al. 2006).

In larger studies comparing ciclesonide treatment with an active control, significant improvements in airflow (changes in FEV_1 and FVC) were reported with ciclesonide and active control in all studies—with the exception of Boulet et al. (2006a) (Table 6). Neither treatment with budesonide nor ciclesonide resulted in improved FEV_1 or FVC; however, the decrease in FVC was significantly less with ciclesonide than with budesonide (P=0.01). The decline in FEV_1 seen with both drugs was expected, since all patients routinely required "moderate" doses of inhaled corticosteroids to control their asthma, were poorly controlled, and had received budesonide 1280 mcg/day during a 2- to 4-week run-in phase, which was stopped prior to randomization to the study regimens. A subsequent abstract by the same authors reported that treatment with ciclesonide 320 mcg once daily and fluticasone propionate 200 mcg twice daily improved FEV_1 to a comparable degree (171 mL and 186 mL, respectively; P<0.0001 vs baseline) (Boulet et al. 2006b).

PEF values were also significantly improved from baseline with ciclesonide and active treatment (Table 6). In one study comparing

Table 6 | Effect on lung function of ciclesonide compared with active treatment in patients aged >12 years with moderate to severe asthma (level 2 evidence; all trials double-blind unless stated)

Treatment (mcg) [duration]	n	Baseline FEV_1 (% of predicted)	Outcome					Reference
			FEV_1 (mL)	FEV_1 (%) change from baseline	FVC (mL)	Morning PEF (L/min)	Evening PEF (L/min)	
CIC 320 qd BUD 400 qd [12 w]	399[a]	50–90	+411[c] +319[c] CIC>BUD (*P*=0.0374)	NR	Increase in both groups (no values given); CIC>BUD (*P*=0.0359)	NR	NR	Biberger et al. 2003
CIC 160 qd FP 88 bid [12 w]	266 263	80–100	+489[c] +499[c]	+20.45 +20.4	+530[c] +499[c]	+33[c] +36[c]	NR	Buhl et al. 2005a
CIC 160 qd A CIC 160 qd P BUD 200 bid [12 w]	139 131 133	≥70	–36[d] (*P*=0.383) +22[d] (*P*=0.598) 0	NR	+5[d] (*P*=0.905) +2[d] (*P*=0.970) 0	–4.4[d] (*P*=0.464) +9.3[d] (*P*=0.131) 0	–1.1[d] (*P*=0.855) +4.0[d] (*P*=0.490) 0	Niphadkar et al. 2005
CIC 160 bid CIC 320 bid FP 440 bid[b] Placebo [12 w]	531[a]	54	NR	+21.24[c] +24.46[c] +30.09[c]	NR	18.11[c] 20.71[c] 31.73[c] –9.69[c]	NR	Weinstein et al. 2005
CIC 320 qd CIC 320 bid BUD 400 bid [8 w]	319[a,e]	NR	NR	NR	NR	+16[c] +24[c] (*P*=0.001 vs BUD) +6[c]	NR	Adachi et al. 2006
CIC 320 bid FP 330 bid [24 w]	528[a,e]	≥80	+11 +38	NR	NR	+36[c] +22[c]	Similar to morning PEF (data shown graphically)	Bateman et al. 2006c
CIC 320 qd BUD 320 qd [12 w]	179 180	65–95	–170 –220	–6 –8	–120 (*P*=0.01 vs BUD) –210	–3[c] –10[c]	–2[c] –4[c]	Boulet et al. 2006a
CIC 320 qd FP 200 bid [12 w]	472[a,e]	60–80	+171 +186	NR	NR	NR	NR	Boulet et al. 2006b
CIC 80 qd CIC 320 qd BUD 200 bid [12 w]	182 195 177	73[c] 72[c] 72[c]	+267[c] +256[c] +355[c]	+10.8 +10.4 +14.4	NR	+12[c] +17[c] +21[c]	NR	Hansel et al. 2006
CIC 640 bid PRED 40 mg qd [2 w]	130[a]	NR	+429 +428	NR	NR	+52[c] +53[c]	NR	Postma et al. 2006

[a]Numbers of patients in each group not specified.
[b]FP dose 37% higher to maintain blinding.
[c]Reported as a mean value.
[d]Least squares mean vs budesonide; intent-to-treat analysis.
[e]Open-label design.
+, increase; –, decrease; A, AM; bid, twice daily; BUD, budesonide; CIC, ciclesonide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FP, fluticasone propionate; NR, not reported; P, PM; PRED, prednisolone; PEF, peak expiratory flow; qd, once daily; w, week.

evening administration of ciclesonide 320 mcg and budesonide 400 mcg, onset of treatment effect as evidenced by daily recordings of morning PEF was observed on day 3 with ciclesonide compared with week 2 with budesonide (Biberger et al. 2003). Differences between ciclesonide and active control were not statistically significant. Similarly, maintenance of pulmonary function with ciclesonide 160 mcg (dosed either in the morning or evening) was not statistically different with budesonide 200 mcg twice daily (Niphadkar et al. 2005). However, an 8-week study reported in abstract form reported a significant difference (P=0.001) in PEF in favour of ciclesonide 320 mcg twice daily compared with budesonide 400 mcg twice daily (Adachi et al. 2006).

These results are predominantly obtained from studies of 12 weeks' duration. In a 40-week open-label extension of a 12-week double-blind study evaluating ciclesonide 800 mcg/day and 1600 mcg/day, the improvement in FEV_1 was sustained throughout the study period (O'Connor et al. 2002). Over a 52-week study period, FEV_1 increased significantly over baseline in patients treated with ciclesonide 200 mcg/day (P=0.0072) and 800 mcg/day (P=0.0237) (Chapman et al. 2002).

Finally, ciclesonide 640 mcg twice daily was as effective as oral prednisolone 40 mg once daily in improving lung function in 130 patients with acute asthma exacerbation, without causing HPA suppression (Postma et al. 2006).

Use of oral corticosteroids

Since the regular use of oral corticosteroids is associated with significant adverse systemic effects, the impact of inhaled corticosteroid therapy on daily oral corticosteroids required to control symptoms in patients with persistent asthma is an important measure of efficacy. Use of inhaled corticosteroids has been associated with a reduction in the use of oral corticosteroids (Larj & Bleecker 2004). In a 12-week trial of 141 patients with severe, persistent asthma, use of ciclesonide significantly reduced the need for oral corticosteroid at doses of 320 or 640 mcg twice daily compared with placebo. Mean percentage change in oral corticosteroid use from baseline was –47.39 (low-dose ciclesonide, P=0.0003 vs placebo), –62.54 (high-dose ciclesonide, P=0.0001 vs placebo), and +4.2 (placebo) (Bateman et al. 2006b).

Asthma symptom score and use of rescue medications

Evidence from large controlled trials that have evaluated ciclesonide and either placebo or a comparator drug indicate that ciclesonide is at least as effective in reducing patient-reported asthma symptoms and use of rescue medications (Table 7). For example, daily albuterol use as rescue medication was reduced significantly in all ciclesonide-treated groups (80, 160, and 320 mcg) but increased in the placebo group (Pearlman et al. 2005). A dose–response effect has been demonstrated, with half as many patients receiving ciclesonide 320 mcg twice daily experiencing an asthma exacerbation compared with those taking ciclesonide 160 mcg/day (23 [6.7%] vs 43 [12.7%] patients) (Bateman et al. 2006a). The higher dose was also associated with significantly lower use of rescue medication (P=0.0005) and improved symptom scores (P=0.0108) than the lower dose.

In one study comparing inhaled doses of ciclesonide 80 mcg once daily, ciclesonide 160 mcg once daily, and fluticasone propionate 88 mcg twice daily in patients with mild-to-moderate persistent asthma, the percentage of days without asthma symptoms and without the need for rescue medications (84–87% for mild disease; 70–79% for moderate disease) was similar for all treatment groups and was highest during the last 4 weeks of the 12-week study (Magnussen et al. 2005). This increase in the last 4 weeks of a 12-week trial was also observed by Buhl et al. (2005b). The percentage of symptom-free days was higher in those patients treated with ciclesonide (91%) than in patients treated with fluticasone (83%, significance not reported), although the percentage of days not requiring rescue medication was comparable (89 vs 91%, respectively) (Buhl et al. 2005b). A full publication of this study by the same authors reported comparable changes in asthma symptom scores for ciclesonide and fluticasone (reductions of 0.75 and 0.86, respectively) (Buhl et al. 2005a). Ciclesonide 320 mcg once daily was comparable to fluticasone 200 mcg twice daily in percentage of days without symptoms (88% both groups) or use of rescue medication (85 and 84%, respectively) after 12 weeks in 472 patients with moderate asthma (Boulet et al. 2006b). Bateman et al. (2006c) adds to the evidence that ciclesonide is equivalent in efficacy to fluticasone.

Patients treated with ciclesonide 160 mcg (dosed either in the morning or in the evening) or budesonide 200 mcg twice daily experienced equivalent periods of symptom-free days (89, 91, and 93%, respectively) (Niphadkar et al. 2005). In addition, other outcomes including rescue medication use, days with control of asthma symptoms, and days without PEF fluctuation were maintained versus baseline with no significant differences between the three groups. In contrast, Adachi et al. (2006) reported significantly lower use of rescue medication (P=0.007) and improved symptom scores (P=0.008) with ciclesonide 320 mcg twice daily compared with budesonide 400 mcg twice daily after 8 weeks' treatment in 319 patients with moderate to severe asthma. Similarly, although overall judged as having comparable efficacy, ciclesonide 320 mcg once daily resulted in significantly more symptom-free days compared with budesonide 320 mcg once daily in 359 patients with persistent asthma (Boulet et al. 2006a).

Use in children

The efficacy of ciclesonide in children has been compared with placebo, budesonide, and fluticasone.

In a large double-blind, randomized trial involving 1031 children aged 4–11 years, mean FEV_1 percent predicted increased by 11.97, 13.58, and 14.17, and mean absolute FEV_1 increased by 250, 280, and 290 mL versus placebo after 12 weeks' treatment with ciclesonide 40, 80, and 160 mcg once daily, respectively (Gelfand et al. 2006). Morning and evening PEF also increased, the latter by 12.27, 18.34, and 15.78 L/min. The changes seen with ciclesonide 80 and 160 mcg/day were significant versus

Table 7 | Effect on symptoms and use of rescue medications of ciclesonide compared with placebo and active treatment in patients with asthma (level 2 evidence; all trials in adults, randomized)

Treatment (mcg) [duration]	n	Baseline FEV_1 (% of predicted)	Outcome		Reference
			Symptom-free days (%)	Use of rescue medication (puffs/day)	
Placebo-controlled trials					
CIC 80 qd CIC 320 qd Placebo [12 w]	360	60–90	Median number of symptom-free days was higher in patients treated with CIC vs placebo	0[a] 0[a] +0.5[a]	Langdon et al. 2005
CIC 80 qd CIC 160 qd CIC 320 qd Placebo [12 w]	257 250 255 249	60–85	NR	–0.86[a] ($P \leq 0.001$) –1.02[a] ($P \leq 0.001$) –1.04[a] ($P \leq 0.001$) +0.42[a]	Pearlman et al. 2005
CIC 320 bid CIC 640 bid Placebo [12 w]	47 49 45	40–80	NR	–0.07[a] –0.08[a] +0.32[a]	Bateman et al. 2006b
Comparator trials					
CIC 320 qd BUD 400 qd [12 w]	399	NR	Similar between groups	Similar between groups	Biberger et al. 2003
CIC 160 qd FP 88 bid [12 w]	266 263	80–100	79 77	–1.00[a] –1.21[a]	Buhl et al. 2004, 2005a,b
CIC 160 qd A CIC 160 qd P BUD 200 bid [12 w]	139 131 133	≥70	89 91 93	Similar between groups	Niphadkar et al. 2005
CIC 320 qd CIC 320 bid BUD 400 bid [8 w]	319	NR	NR	NR –0.44[c] NR	Adachi et al. 2006
CIC 320 bid FP 330 bid [24 w]	528	≥80	Similar between groups	Similar between groups	Bateman et al. 2006c
CIC 320 qd BUD 320 qd [12 w]	179 180	65–95	43.6[d] 25.8	57.5[b] 53.6[b]	Boulet et al. 2006a
CIC 320 qd FP 200 bid [12 w]	472	60–80	88 88	89[b] 88[b]	Boulet et al. 2006b
CIC 80 qd CIC 320 qd BUD 200 bid [12 w]	182 195 177	73 72 72	Approx. 40% for all treatment groups	–0.68[a] ($P<0.001$) –1.00[a] ($P<0.001$) –1.04[a] ($P<0.001$)	Hansel et al. 2006
CIC 640 bid PRED 40 mg qd [2 w]	130	NR	Similar between groups	Similar between groups	Postma et al. 2006

[a]Change from baseline.
[b]Percentage of days without use.
[c]$P=0.029$ vs CIC 320qd, $P=0.007$ vs BUD.
[d]$P=0.017$.
+, increase; –, decrease; bid, twice daily; A, AM; BUD, budesonide; CIC, ciclesonide; FEV_1, forced expiratory volume in 1 s; FP, fluticasone propionate; NR, not reported; P, PM; qd, once daily.

Table 8 | Effect on quality of life of ciclesonide compared with placebo or active treatment (level 2 evidence; all studies randomized, multicenter, double-blind, parallel-group, placebo-controlled, 12 weeks' duration)

Treatment (mcg)	n	Baseline FEV_1 (% of predicted)	Outcome: patients achieving an MID (≥0.5) in QOL score (%)	Reference
Studies in adults and adolescents aged >12 years				
CIC 160 bid	531	40–65	42.5	Bernstein et al. 2005
CIC 320 bid			43	
FP 440 bid[a]			58.8	
Placebo			26.8	
CIC 80 qd	1015	60–85	47	Nayak et al. 2005
CIC 160 qd			50	
CIC 320 qd			50.6	
Placebo			31	
Study in pediatric patients aged 7–17 years				
CIC 40 qd	793	60–85	46.1	Miller et al. 2005; Gelfand et al. 2006
CIC 80 qd			50	
CIC 160 qd			52.5	
Placebo			36.5	
CIC 160 qd	340	NR	53.8	Vermeulen et al. 2006
BUD 400 qd	173		50.6	

[a]FP dose 37% higher to maintain blinding.

bid, twice daily; BUD, budesonide; CIC, ciclesonide; FEV_1, forced expiratory volume in 1 s; FP, fluticasone propionate; MID, minimally important difference; qd, once daily.

placebo. These improvements were associated with significantly more symptom-free days among children receiving ciclesonide 80 (52.44%; $P<0.0001$) and 160 mcg/day (48.77%; $P=0.0139$) compared with placebo (42.52%), and significantly lower use of rescue medication ($P<0.01$). Ciclesonide improved symptom scores and reduced nighttime awakening at all three doses.

There is evidence that ciclesonide 160 mcg/day, given either as a single dose or as 80 mcg twice daily, is as effective as fluticasone 88 mcg twice daily and budesonide 400 mcg once daily. In 556 children, ciclesonide and fluticasone increased mean FEV_1 by 298 and 297 mL, respectively, after 12 weeks (Pedersen et al. 2004a). Corresponding increases in mean morning and evening PEF were 31 and 29 L/min with ciclesonide, and 34 and 29 L/min with fluticasone.

Mean FEV_1 increased by 220 mL in 340 children aged 6–11 years following 12 weeks' treatment with ciclesonide and by 253 mL in 173 receiving budesonide (von Berg et al. 2006). Asthma symptoms were absent in an almost identical proportion of days in each group (74% for ciclesonide and 73% for budesonide), and both drugs were comparable in improving symptom scores and reducing rescue medication use.

Quality of life

HRQOL measures offer an important patient perspective into the therapeutic management of asthma. Because asthma is a chronic disease that may affect a patient's ability to participate in normal daily activities including work, school, and extracurricular activities, it is important to include the impact of a medication on quality of life in a determination of its effectiveness and place in therapy. There is often a disconnection between medication-induced changes in airways as assessed by the clinician and patient perceptions of their functional status. The effect of treatment on HRQOL is now recognized as an important gauge of therapy and should be used as a determinant of treatment effect. HRQOL measurement provides the clinician with important insight into the burden of disease and provides an appreciation of the effect of treatment on functional status. Treatments with positive HRQOL effects may improve patient compliance with therapy and improve overall patient satisfaction (Gerth van Wijk 2005).

Although several HRQOL tools have been used to evaluate HRQOL in patients with asthma, in the ciclesonide studies that provided HRQOL information, the Asthma Quality of Life Questionnaire (AQLQ) and the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) were the tools used for assessment. The reliability and validity of the AQLQ has been verified in several studies (Gupchup et al. 1997; van der Molen et al. 1997; Sanjuas et al. 2002). The AQLQ is a 32-item, four-domain (symptoms, emotional function, activity limitation, and breathlessness) questionnaire that can be interviewer- or self-administered. Using this questionnaire, a change in score of 0.5 is considered the minimum change necessary for clinical significance.

A separate pediatric-based questionnaire is necessary for children because it is clear that conventional measures of the effectiveness of therapy (asthma severity, spirometry, and medication use) and parents' perceptions of a child's functionality weakly correlate with how children actually feel and their ability to participate in activities of daily life (Juniper et al. 1996).

The PAQLQ is a 23-item questionnaire that is appropriate for children between the ages of 7 and 17 years and focuses on three domains (symptoms, emotional function, and activity limitation). A change in score of 0.5 reflects a minimally important difference. Both interviewer- and self-administration formats of the PAQLQ are available (Juniper 1997).

The impact of ciclesonide on the HRQOL of patients with asthma has been assessed (Table 8) (Bernstein et al. 2005; Miller et al. 2005; Nayak et al. 2005). In one study that included patients with severe persistent asthma (FEV_1 40–65%), clinically significant changes in AQLQ (≥0.5) were noted in all three groups receiving ciclesonide 160 or 320 mcg, or fluticasone 440 mcg twice daily (Bernstein et al. 2005). The change in AQLQ with fluticasone was greater than that noted with either dose of ciclesonide, although the statistical significance of this difference was not reported. These HRQOL studies were only conducted for a period of 12 weeks, therefore, it is not known if improvements in QOL are sustainable or whether the changes translate to significant long-term patient improvement.

Tolerability

A major component of the rationale for the development of ciclesonide is the minimization of local and systemic side effects often experienced with inhaled corticosteroids. Ciclesonide has been well tolerated in clinical trials with most adverse effects reported as mild. It is anticipated that the airway activation of ciclesonide will reduce the incidence of adverse effects compared with currently available inhaled corticosteroids. Although there are some data from longer term studies, the bulk of the evidence supporting the lack of systemic effects with ciclesonide therapy is limited to 12 weeks of treatment. Further long-term data will be necessary to confirm if ciclesonide offers an advantage over the other inhaled corticosteroids.

Local adverse effects

Local adverse effects associated with the use of inhaled corticosteroids include perioral dermatitis, tongue hypertrophy, cough during inhalation, and sensation of thirst. The most frequently reported clinically significant effects are oropharyngeal candidiasis and dysphonia (Roland et al. 2004). Deposition of active medication in the oropharyngeal cavity is dependent on the delivery device and can be decreased with the use of spacers. These adverse effects, while they are not considered to be clinically serious, are troublesome and may affect patient adherence (Goeman 2002).

Oropharyngeal deposition of ciclesonide (metered-dose inhaler with hydrofluoroalkane propellant) is reduced compared with fluticasone (metered-dose inhaler with hydrofluoroalkane propellant) and budesonide (metered-dose inhaler with CFC) (Nave et al. 2005a; Richter et al. 2005). This reduction in oral deposition is expected to correlate with a lower rate of local adverse effects. In a pooled analysis of phase II and phase III studies, data from 12 251 patients who received ciclesonide (n=7706), active control [budesonide, beclomethasone, or fluticasone (n=3330)], or placebo (n=1215) for 12 weeks were analyzed to determine the incidence of oropharyngeal adverse events (candidiasis, hoarseness, cough) (Engelstätter et al. 2005). The incidence of local adverse events per patient year was similar in the ciclesonide and placebo group; oral candidiasis and hoarseness occurred less frequently in the ciclesonide group compared with the active control group (*P* value not reported) (Table 9). In a subanalysis, fewer patients in the ciclesonide group experienced an oral adverse event compared with patients in the fluticasone subgroup ($P<0.0001$).

Table 9 | Incidence of oropharyngeal adverse events with ciclesonide compared with placebo or active treatment[a] (adapted from Engelstätter et al. 2005)

Adverse event	Incidence of event/patient year		
	Ciclesonide	Placebo	Active control[b]
Candidiasis	0.02	0.02	0.07
Hoarseness	0.03	0.03	0.07

[a]Cough not reported.
[b]Beclomethasone, budesonide, or fluticasone.

There is limited evidence that this lower frequency of oral adverse effects is maintained when treatment exceeds 12 weeks. A single open-label study that followed a 12-week placebo-controlled trial reported oropharyngeal side effects in 10 of 228 patients treated with ciclesonide (3.5%) (Chapman et al. 2002). After 24 weeks of treatment in an open-label study involving 528 patients, oral candidiasis or dysphonia were reported by 5.1% of patients receiving ciclesonide 320 mcg twice daily, significantly less than the 12.8% for fluticasone 330 mcg twice daily ($P=0.0014$) (Bateman et al. 2006c).

Systemic adverse effects

Systemic effects of inhaled corticosteroids occur because a large percentage (80%) of an administered dose of active drug is swallowed (Roland et al. 2004). Additional systemic exposure can occur as the drug is absorbed from the pulmonary fluid into the systemic circulation (Hübner et al. 2005). The amount of drug that is available to the systemic circulation, method of delivery, and lipophilicity of the drug influence risk of systemic side effects. The extent of systemic exposure with inhaled corticosteroids is typically reported by the magnitude of HPA axis suppression, serum and urinary cortisol concentrations, and effects on bone growth or mineralization. Systemically active corticosteroids bind to glucocorticoid receptors in the hypothalamus and adrenal pituitary causing a decrease in the amount of corticotropin-releasing hormone and adrenocorticotropic hormone leading to decreased cortisol secretion (Lipworth et al. 2005).

HPA axis suppression and cortisol levels

There is clear evidence that ciclesonide does not cause HPA axis suppression after 12 weeks of treatment.

In a 12-week, double-blind, randomized, placebo-controlled study assessing the systemic adverse effect potential of ciclesonide, 164 patients were randomized to receive fluticasone propionate (CFC propellant) 440 mcg daily, ciclesonide 320 mcg once daily, ciclesonide 320 mcg twice daily, or placebo (Lipworth et al. 2005). Serum and urine cortisol levels were measured at baseline, week 6, and week 12. HPA axis function was preserved with ciclesonide in doses of up to 640 mcg/day. After 12 weeks, changes in mean peak serum cortisol levels and 24-hour urinary free cortisol levels following both doses of ciclesonide were not significantly different from placebo, in contrast to fluticasone propionate 880 mcg/day, which was associated with significant reductions of 9–10% in peak serum cortisol levels and 60% in 24-hour urinary free cortisol levels (Lipworth et al. 2005). Other studies have also reported a lack of effect of ciclesonide therapy on serum and 24-hour urinary free cortisol corrected for creatinine (Postma et al. 2001; Pearlman et al. 2005).

In a 12-week study of once-daily inhaled ciclesonide 80 mcg (n=182) or 320 mcg (n=195) compared with inhaled budesonide 200 mcg (n=177) twice daily, no relevant changes in 24-hour urinary cortisol excretion were observed in patients receiving ciclesonide. However, patients who received budesonide had a statistically significant suppression of urine cortisol ($P<0.05$) (Hansel et al. 2006).

Sixty adult patients were randomized in a single-center, double-blind, double-dummy, parallel-group study evaluating HPA axis suppression associated with the use of ciclesonide compared to fluticasone in patients with moderate-to-severe asthma (Szefler et al. 2005). Patients received either ciclesonide 320 mcg twice daily, ciclesonide 640 mcg twice daily, fluticasone 440 mcg twice daily, fluticasone 880 mcg twice daily, or placebo for 29 days. Mean serum cortisol $AUC_{0–24h}$ at the end of treatment was significantly suppressed in the high-dose fluticasone group. A cosyntropin stimulation test showed no statistically significant differences among the groups. Twenty-four-hour urinary cortisol levels were significantly increased from baseline at week 4 compared with placebo in the ciclesonide 320 mcg twice-daily group ($P=0.0224$; 95% confidence intervals 0.0023, 0.0283); the other treatment groups did not demonstrate any change in urinary cortisol levels (Szefler et al. 2005).

In addition, two abstracts report preliminary information on HPA axis suppression with ciclesonide and an active control in adults (Ukena et al. 2003) and in children (Pederson et al. 2004b). In the study comparing ciclesonide 320 mcg/day with budesonide 400 mcg/day in adults, no relevant change in laboratory parameters or urine cortisol were noted after 12 weeks of treatment (Ukena et al. 2003). In the pediatric phase III comparator study, the difference between urinary free cortisol levels in patients treated with ciclesonide 80 mcg twice daily (+1.54 nmol/mmol creatinine) versus patients treated with fluticasone propionate 88 mcg twice daily (–1.83 nmol/mmol creatinine) was statistically significant ($P=0.0062$) (Pedersen et al. 2004b).

The lack of suppressive effect appears to be independent of dose. A study of high-dose ciclesonide 800 mcg/day substantiates the lack of suppressive effect with ciclesonide. The HPA axis function of 12 healthy volunteers was preserved after 800 mcg/day of inhaled doses of ciclesonide (400 mcg twice daily, 800 mcg in the morning, or 800 mcg in the evening) given for 7 days. The effect was independent of time of administration (Weinbrenner et al. 2002). There is further evidence for the lack of effect on HPA axis from 26 patients with asthma receiving ciclesonide 320 mcg once daily, or 640 mcg once or twice daily, or fluticasone 440 mcg or 880 mcg twice daily in randomized, double-blind fashion for 9 days (Derom et al. 2005). Although the study was short duration and involved few patients, 24-hour cortisol secretion was unaffected by ciclesonide, even at the high dose.

Furthermore, there is evidence that HPA axis suppression does not appear to develop with longer-term ciclesonide treatment (Chapman et al. 2002; O'Connor et al. 2002). In these placebo-controlled ciclesonide trials, patients received an individualized dose of ciclesonide for 40 weeks following the initial 12-week study. Serum cortisol levels were increased compared with the former steroid treatment (budesonide 800–2000 mcg/day or equivalent) (O'Connor et al. 2002). There was no evidence that ciclesonide suppressed the HPA axis as evidenced by changes in serum and urine cortisol measurements (Chapman et al. 2002). Importantly, these long-term data have been replicated in 661 children aged 5–8.5 years, with ciclesonide 40 or 160 mcg/day associated with minimal changes in urinary-free cortisol levels after 1 year of treatment (Bernstein et al. 2006).

Bone mineralization and growth

Orally administered glucocorticoids are known to affect bone mineralization, decrease osteocalcin concentration in healthy volunteers, and decrease bone density in the lumbar spine (Jones et al. 2002; van Staa et al. 2002). In young patients, these factors impact bone growth. In adults, these effects can increase the risk of fracture. Glucocorticoids assert their effect on bone predominantly by decreasing bone formation through a negative effect on the function and lifespan of osteoblasts (Jones et al. 2002). Despite the limited systemic absorption of inhaled corticosteroids, the long-term administration of these agents is also believed to impact bone metabolism (Roland 2004; O'Connell 2005). Laboratory indices of bone formation (bone-specific alkaline phosphatase and serum osteocalcin) have been followed to quantify the impact of therapy.

Over a 52-week study in patients with moderate-to-severe asthma, increased levels of serum bone-specific alkaline phosphatase and serum osteocalcin were observed in patients after receiving ciclesonide compared with the levels obtained while they were on their prestudy doses of steroid ($P<0.05$), suggesting that the impact of ciclesonide treatment on bone metabolism in these patients was significantly less than the effects of previously used inhaled corticosteroid therapies (O'Connor et al. 2002).

Studies measuring the effect of lower leg growth in children have been reported. Twenty-four children aged 6–12 years were randomized to receive a daily dose of ciclesonide 40 mcg, 80 mcg, 160 mcg, or placebo over a 12-week period. No statistically significant differences in knemometry results, height

measurements, or HPA suppression occurred in any of the patients (Agertoft & Pedersen 2005). Growth velocity was unaffected by 1 year of treatment with ciclesonide in 661 children aged 5–8.5 years (Skoner et al. 2006). During treatment, mean linear growth velocity was 5.73 cm/year with ciclesonide 40 mcg/day, 5.6 cm/year with ciclesonide 160 mcg/day, and 5.75 cm/year with placebo. In the same patient cohort, ciclesonide also had no effect on skeletal maturity, as measured by chronologic to bone age ratio (Neffen et al. 2006). A shift from normal to high ratio was seen in 17 patients, although a treatment-related effect seems unlikely since fewer of those taking higher-dose ciclesonide were affected (1.1%), and the incidence with low-dose ciclesonide was similar to that with placebo (4.3 and 4%).

Drug interaction potential

The pharmacokinetic properties of ciclesonide are such that significant drug–drug interactions are not expected with its use. Ciclesonide is activated in airways at the desired site of action and very little of the drug is available to the systemic circulation. A single pharmacokinetic study evaluating ciclesonide and erythromycin coadministration demonstrated a lack of interaction between these medications (Nave et al. 2005b). As with other inhaled corticosteroids, drug–drug interactions are not considered to be a clinical concern.

Resource utilization

At present, economic evidence comparing the use of ciclesonide with other inhaled corticosteroids is not available. Ciclesonide, from a clinical standpoint, appears comparable to budesonide and fluticasone propionate, but with less propensity for systemic adverse effects. It is possible that the once-daily administration of ciclesonide coupled with its low adverse event profile will give ciclesonide an advantage over other inhaled corticosteroids. Use of ciclesonide over one of the other inhaled corticosteroids will ultimately depend on additional long-term data as they become available, including its long-term adverse effect profile and impact on HRQOL. Economic data, including the effect of ciclesonide treatment on both direct and indirect medical costs, will need to be factored into the decision-making process to determine its place in therapy with regard to the other inhaled corticosteroids.

In general, inhaled corticosteroids are considered the most effective therapy for reducing asthma exacerbations and studies have reported that the use of these agents reduce medical costs and decrease the use of healthcare resources (Halpern 2003). A recent meta analysis examined the long-term effects of inhaled corticosteroids, long-acting beta$_2$ agonists, leukotriene pathway modifiers/receptor antagonists, and antiimmunoglobulin E antibody therapies. Of these agents, inhaled corticosteroids were found to have the greatest impact on the reduction of asthma exacerbations (55% vs placebo; relative risk 0.46, 95% confidence intervals 0.34, 0.62; $P<0.001$) (Sin et al. 2004). These reductions in exacerbations translate to economic savings from decreased hospitalizations, decreased emergency room visits, and a decrease in physician visits and use of rescue medications. In order for an inhaled corticosteroid to produce its positive effects, it must be used continuously to keep the inflammatory process in check.

Patient group/population

Asthma affects all age groups, from pediatric patients to the elderly. Available evidence for ciclesonide demonstrates efficacy in patients with persistent asthma that is similar to other currently available inhaled corticosteroids. Inhaled corticosteroids are the mainstay of treatment for patients with persistent asthma. Any patient with symptom frequency that suggests persistent disease would benefit from maintenance treatment with an agent such as ciclesonide. The evidence for a lack of effect on growth rate and skeletal maturation in children in the long term (1 year) indicates that ciclesonide is suitable for pediatric use.

Dosage, administration, and formulations

Ciclesonide (Alvesco®) is available in a 80 mcg and 160 mcg metered-dose inhaler, with hydrofluoroalkane propellant. Approved dosages and indications vary between different countries, and readers are advised to consult their local prescribing information (Anon. 2006). The recommended starting dose is usually 160 mcg once daily, preferably in the evening. Maintenance on 80 mcg once daily may be effective in some patients. No dosage adjustment is necessary in the elderly or in patients with hepatic or renal impairment.

Place in therapy

The unique pharmacokinetic profile of ciclesonide confers a potential advantage in that there is minimal systemic absorption of active drug, which appears to be sustained as shown by a lack of HPA axis suppression after 1 year of treatment. Further evidence will confirm if efficacy is sustained in the longer term with approved doses, and if the decrease in systemic exposure is linked to an overall increased safety profile. The decrease in adverse effects that have been observed in short-term trials may be beneficial in some patients for whom the local effects are bothersome and may lead to disruptions in therapy. In addition, patients with more severe disease who are being treated with higher doses of inhaled corticosteroids may also benefit because of the apparent decrease in systemic exposure associated with ciclesonide use. The drug appears to have a role in the management of pediatric patients with asthma, and is not associated with growth retardation in long-term use.

The available evidence indicates that ciclesonide is as effective as fluticasone and budesonide for the management of persistent asthma, as shown by improvements in lung function parameters, symptom scores, and use of rescue medications. Inhaled corticosteroids are considered to be the foundation of asthma management in patients with persistent disease (Table 2). It is expected that ciclesonide will be included in updated guidelines as a primary therapy along with other inhaled corticosteroids. Currently, the use of combination inhalers

(beta-agonist/corticosteroid) is recommended as a means to streamline therapy in patients with persistent asthma. (Anon. 2005b; British Thoracic Society 2005). Ciclesonide is not available in a combination formulation and therefore patients would be required to have two separate inhalers. There is evidence that lung function improvements are maintained for up to 1 year of treatment.

The impact of ciclesonide use on overall disease course, DALYs, and hospitalization rate as compared with other currently available inhaled corticosteroids has not been reported. These measures are important to the overall evaluation of the expected role of ciclesonide in the management of persistent asthma.

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