



Ciclesonide: a novel inhaled corticosteroid for the treatment of persistent asthma – a pharmacologic and clinical profile

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Inhaled corticosteroids are recommended first-line therapy for asthma of all severities. Concerns regarding local and systemic side effects can influence adherence, and subsequently, efficacy and long-term asthma control. Ciclesonide is a novel inhaled corticosteroid with an improved therapeutic margin – its efficacy is similar to that of other inhaled corticosteroids, but with a potentially better local and systemic safety profile in patients with persistent asthma. Ciclesonide is activated, mainly in the lung, to desisobutryl-ciclesonide, the active metabolite, which, together with its other pharmacokinetic properties, contributes to its improved safety profile. Additionally, the drug is delivered through a hydrofluoroalkane metered-dose inhaler, which allows high lung deposition and delivery into the small airways. The improved therapeutic margin of ciclesonide may increase patient adherence, thereby ultimately improving asthma control.

Asthma is currently one of the most prevalent diseases in the USA and worldwide, and its prevalence has increased in recent years [1,2,101]. Approximately 15 million individuals in the USA (5–6% of the population), including 5 million children and 300 million people worldwide, have this disease [3–5]. Asthma is responsible for approximately 5500 deaths in the USA and 180,000 deaths worldwide each year [2,3,101]. The disease is also associated with significant direct and indirect costs, relating to more than 28 million lost school or work days annually in the USA [1–4]. Other related costs include those associated with emergency room visits, hospitalizations and reduced work productivity.

Currently, there are a number of therapeutic agents available for the management of asthma. Of these, inhaled corticosteroids (ICSs) are recommended as first-line therapy for infants, children and adults with persistent asthma of all severities [2,6]. Several ICSs are currently commercially available, including fluticasone propionate, budesonide and beclomethasone dipropionate. Although all these agents are efficacious, their pharmacokinetic properties differ greatly, potentially affecting safety profiles and dosing regimens [5,7,8]. A number of other ICSs are also under development, including ciclesonide and mometasone furoate, both of which have the potential to be delivered once daily [9,10]. These agents are expected to provide asthma patients with additional options for disease management.

Unmet needs with currently available ICS therapy

Asthma is a chronic inflammatory disease associated with a high rate of morbidity and mortality. Therefore, the primary goal of asthma treatment, as defined by recent guidelines, is the achievement and maintenance of long-term control [2,6], with minimal symptoms and near-normal lung function (as measured by forced expiratory volume in one second [FEV₁], peak expiratory flow [PEF] and forced vital capacity [FVC]). Other valuable endpoints include changes in asthma exacerbations, night-time awakenings and the use of rescue medication.

As with many chronic diseases, gaining long-term control requires adherence to treatment, which can be challenging. The degree to which patients will adhere to their asthma therapy is influenced by several factors, including the frequency of dosing regimen, ease of use of the delivery device and the safety profile of the particular drug [11]. Therefore, therapies that address the potential for poor adherence and are efficacious and well tolerated, could improve the prognosis for the long-term treatment of patients with asthma [12].

Safety considerations & their impact on adherence & asthma control with ICS therapy

Although ICSs are associated with fewer side effects than oral corticosteroids, clinically relevant safety complications are still a concern [13].

Keywords: asthma, ciclesonide, des-ciclesonide, efficacy, pharmacokinetics, safety



Related side effects include local oropharyngeal effects and potentially more serious systemic effects associated with cortisol suppression, which are linked to oral and pulmonary bioavailability of the drug. These concerns regarding potential toxicities have resulted in some reluctance among physicians to prescribe ICSs, despite the fact that these drugs are proven the most effective long-term therapy for the control of persistent asthma [14].

The occurrence of local oropharyngeal side effects such as oral candidiasis and dysphonia are influenced by the duration and dosage of the ICS [15], while systemic adverse effects become apparent when recommended therapeutic doses of ICSs are exceeded [14,16,17]. Based on the pharmacology of the drug class, oral candidiasis is thought to be due to the immunosuppressive action of the ICS [15]. Similarly, dysphonia (alone or in association with a sore throat) is a notable local side effect observed with the long-term use of an ICS [15].

Systemic effects linked with ICS use include hypothalamic–pituitary–adrenal (HPA)-axis suppression and untoward effects on growth velocity (in children), skin, eyes and bone metabolism [5,18]. These effects are associated with long-term exposure, in particular with the higher doses of ICSs required to control severe asthma. The occurrence of these adverse events is influenced by several factors – including the specific drug (e.g., the affinity of the ICS for the glucocorticoid receptor), delivery device, dosage and individual patient characteristics – and may negatively affect patient quality of life [15,19].

Local and systemic side effects can also result in patients discontinuing treatment, which in turn can lead to a deterioration in asthma control [11,101]. These side effects may be of greater concern among patients with severe asthma who are more dependent on continued ICS therapy for optimal control.

The ‘ideal’ ICS for the treatment of patients with asthma

It is therefore proposed that the ‘ideal’ ICS would provide effective asthma control via a convenient dosing regimen and device with several pharmacologic properties that minimize oral and systemic exposure and provide optimal efficacy and safety. This ‘ideal’ ICS should be active only within the lung, possess a high degree of glucocorticoid-receptor affinity and have a high pulmonary retention time (lipid conjugation provides a reservoir for the slow release of active compound).

It should also possess low systemic exposure, which can be achieved through several pharmacokinetic characteristics including high protein binding and a high clearance rate. An ICS with this profile would be a valuable addition to the treatment options for patients with asthma [5].

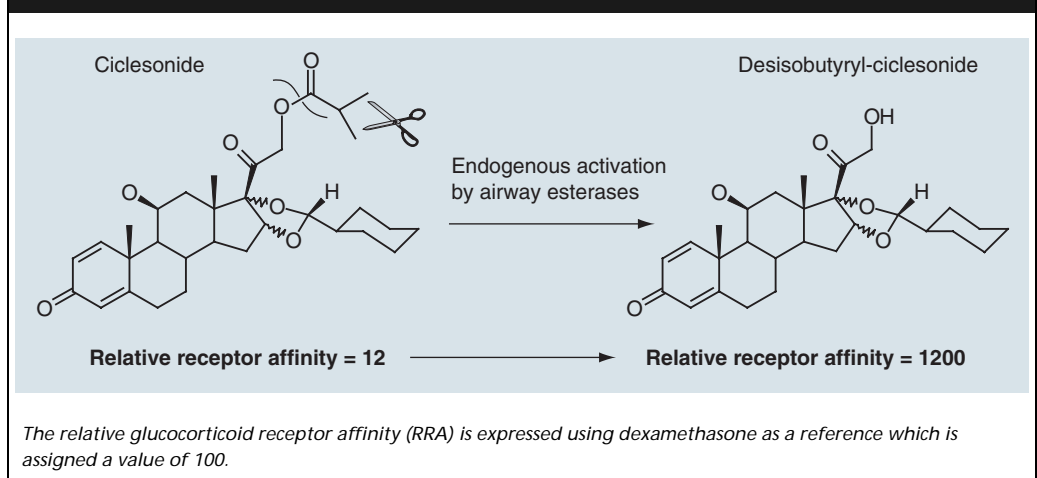
Introduction to the compound

Ciclesonide is a novel ICS with demonstrated efficacy and minimal side effects in a number of clinical studies [10,20–27]. It is formulated as a hydrofluoroalkane metered-dose inhaler (HFA-MDI) which results in high lung deposition so that inflammation in the small airways can be potentially targeted [28]. Ciclesonide itself is inactive and is converted to the active metabolite, desisobutyryl-ciclesonide (des-ciclesonide), primarily in the lung [29]. Ciclesonide possesses a number of unique pharmacokinetic and pharmacodynamic properties that contribute to an improved therapeutic margin compared with other currently available ICSs [7,29,30]. Additionally, this ICS has the potential for a once-daily dosing regimen in adults with mild-to-moderate persistent asthma and in children with all severities of persistent asthma, which may help to improve treatment adherence, and ultimately, asthma control.

Chemistry

Ciclesonide ($C_{32}H_{44}O_7$, molecular weight 540.7) is a nonhalogenated ICS [30,31]. There are two epimers, but only the most potent one, the *R*-epimer, was developed for clinical use [32,33]. Ciclesonide is the 2′*R*-epimer of 2′-cyclohexyl-11β-hydroxy-21-isobutyryloxy-16b*H*-dioxolo(5′,4′:16,17)pregna-1,4-diene-3,20-dione (Figure 1) [32].

Ciclesonide is a white/yellow-white powder that is soluble in dehydrated ethanol, acetone, dichloromethane and chloroform. Enzymatic cleavage converts ciclesonide (the parent compound) into the active primary metabolite, des-ciclesonide (Figure 1) [31]. *In vitro* studies have demonstrated that following 24 h incubation of rodent rat slices with ciclesonide there was complete conversion to des-ciclesonide (74.2%) and des-ciclesonide fatty acid conjugates (25.8%) [34,35]. Importantly, pharmacokinetic studies revealed that [^{14}C]-ciclesonide is not retained in red blood cells [31]. It is formulated as a solution in the propellant hydrofluoroalkane (HFA-134a [1,1,1,2-tetrafluoroethane]) and ethanol and has been developed for delivery via a pressurized MDI.

Figure 1. Structure of ciclesonide and its active metabolite desisobutyryl-ciclesonide.

Pharmacologic properties

The efficacy and safety of an ICS can be influenced by several pharmacologic factors. Efficacy is affected by such factors as: the potency of the molecule (assessed as relative receptor binding affinity [RRA] versus dexamethasone, which is assigned a value of 100); delivery and higher lung deposition characteristics; lipophilicity and lipid conjugation [7,36,37]. The safety profile of an ICS is also affected by the potency of the molecule, as well as several important factors relating to systemic side effects, such as oral bioavailability, clearance rate and plasma protein binding (Figure 2) [7,36,37].

Absorption

Total systemic ICS bioavailability is calculated as the sum of the oral bioavailability (the amount of ICS that becomes systemically available after being swallowed) and the fraction available to the lungs (pulmonary deposition) [5,7]. Data suggest that the oral bioavailability of both ciclesonide and its active metabolite, des-ciclesonide, are less than 1% [31], which is similar to the oral bioavailability for fluticasone propionate [7,38]. A clinical study examining the extent of oropharyngeal deposition of both inhaled ciclesonide (640 µg ex-actuator) and des-ciclesonide combined was shown to be only about 53% of that of fluticasone propionate 880 µg after administration via HFA-MDI. In addition, only 8% of des-ciclesonide relative to fluticasone propionate was present in the oropharynx [39]. Similar findings have been reported in healthy volunteers where the sum of oropharyngeal deposition of inhaled ciclesonide (640 µg ex-actuator) and des-ciclesonide was 47% of that of budesonide (800 µg Pulmicort®) [40].

ICSs that are formulated as solutions, such as ciclesonide, have been shown to have a smaller particle size than suspensions, which is likely to improve lung deposition characteristics [41]. Particles with a small (<5 µm) mass median aerodynamic diameter (MMAD) are considered to be the most appropriate for lower airway deposition [42]. The MMAD for ciclesonide delivered by HFA-MDI has been shown to be between 1 and 2 µm [41]. The pulmonary deposition for ciclesonide is approximately 50% of the delivered dose, as demonstrated in healthy subjects [43]. Similarly high levels of lung deposition have been observed in patients with asthma [44]. Use of the AeroChamber® Plus (3M Pharmaceuticals) spacer with the ciclesonide-MDI does not affect the pharmacokinetics of the active metabolite des-ciclesonide, and therefore patients may benefit from using a spacer without compromising lung deposition [45].

Distribution

The fraction of ICS that is deposited in the lung eventually appears in the systemic circulation, where it has the potential to cause systemic adverse effects by interacting with glucocorticosteroid receptors outside the lung. Thus, rapid removal of freely circulating ICS reduces the potential to elicit these effects. Strong plasma protein binding is a desirable property for any ICS as there will be a low proportion of unbound drug in the circulation to interact with systemic receptors [5,7,8].

Des-ciclesonide has a large volume of distribution, as does fluticasone propionate [5,30]. Both ciclesonide and its active metabolite have been shown to be highly protein bound – approximately

the ICSs [50]. The values for ciclesonide and des-ciclesonide are 2 to 4 times greater than for budesonide [51].

Des-ciclesonide, budesonide and fluticasone propionate have relatively long elimination half-lives – 3.5, 2.8 and approximately 8 h, respectively – after intravenous administration compared with beclomethasone dipropionate [5,31,37,41]. Healthy volunteer studies have shown that following oral or intravenous administration of [¹⁴C]-ciclesonide, the mean cumulative excretion of total radioactivity was almost complete at 120 h [31]. Finally, fecal excretion was the predominant route of elimination of total radioactivity after both methods of drug administration [31].

The pharmacologic properties of ciclesonide indicate that it may have the potential to provide an advancement in the design of ICSs for treating persistent asthma, compared with currently available drugs.

Clinical profile

Ciclesonide administered via HFA-MDI has proven clinical efficacy in patients with persistent asthma, across a range of severities, as assessed by improvements in FEV₁, PEF and FVC, reductions in asthma symptom scores and reductions in airway hyper-responsiveness [10,21,22,52–62]. A series of studies of patients with persistent asthma have compared the efficacy and safety of ciclesonide with placebo and active comparators, fluticasone propionate or budesonide [20–22,61]. These data support the benefits of the pharmacologic properties of ciclesonide in the treatment of asthma. In the following sections, all doses of ciclesonide are expressed as ex-actuator.

Placebo-controlled studies

Clinical efficacy in mild-to-moderate asthma

Several controlled, dose-ranging, 12-week studies examined the effects of ciclesonide 80, 160, 320 or 640 µg once daily on lung function in patients with mild-to-moderate persistent asthma compared with placebo [53–55,62].

In one 12-week study (n = 360), ciclesonide 80 and 320 µg once daily significantly increased morning PEF compared with placebo (2.0 l/min, p = 0.0012 and 3.0 l/min, p = 0.0006 for ciclesonide 80 and 320 µg once daily, respectively, versus -18 l/min for placebo) in adult patients with persistent asthma [54].

In another 12-week, placebo-controlled study followed by an open-label period of 40 weeks, the efficacy of ciclesonide 160 and 640 µg once daily was evaluated in 329 adults with asthma [52,53].

At the end of the initial 12-week treatment period, FEV₁ was significantly higher in both ciclesonide groups compared with placebo (p = 0.007 and p ≤ 0.02 for ciclesonide 160 and 640 µg per day, respectively, versus -144 ml for placebo) [53]. In addition, the proportion of patients completing the study without showing 'lack of efficacy' was significantly greater for ciclesonide-treated patients compared with placebo (p < 0.0001) [53]. Furthermore, during the 40-week open-label phase of the extension study, FEV₁ improved significantly in placebo (p = 0.0001) and both treatment groups (p = 0.0133 and p = 0.0003 for ciclesonide 160 and 640 µg per day, respectively) [52].

The effects of morning and evening doses of ciclesonide 160 µg once-daily on lung function were evaluated in a randomized, double-blind, parallel-group study in 209 adults with mild-to-moderate persistent asthma [10]. After 8 weeks of treatment with ciclesonide, clinically relevant improvements were reported in evening PEF in both the morning and evening treatment groups (7 l/min [p = NS versus baseline] and 16 l/min [p < 0.05 versus baseline]). Asthma symptoms improved significantly in both treatment groups (morning -0.38 and evening -0.50, p < 0.001), and there was a reduction in the use of rescue medication in both the morning and evening treatment groups (-0.36 puffs/24 h for both, p < 0.05). These results indicate that ciclesonide can be administered at either time of the day [10].

Collectively, these studies have demonstrated that ciclesonide 80, 160, 320 or 640 µg per day is more effective in the short and long term in the treatment of patients with mild-to-moderate asthma compared with placebo, providing significant improvements in lung function and asthma symptoms.

Clinical efficacy in moderate-to-severe asthma

The use of higher doses of ciclesonide (640 or 1280 µg per day) in 365 patients with moderate-to-severe asthma has also been examined in a 12-week study followed by a 40-week open-label period [58,59]. Patients had been pretreated with beclomethasone dipropionate (800–2000 µg per day). Following a 2-week baseline period in which patients were treated with beclomethasone dipropionate (1600 µg per day), patients were randomized to one of the two ciclesonide dosages. During the randomized, double-blind, 12-week study period, ciclesonide improved the lung function parameters FEV₁ and PEF, and reduced asthma symptom scores and use of rescue

medication. Following 12 weeks of treatment, morning PEF increased by 5% in both ciclesonide groups compared with baseline ($p = 0.0002$ and $p = 0.001$ for ciclesonide 640 and 1280 μg per day, respectively). Compared with baseline, FEV_1 also increased significantly, although this increase was not dose-related (640 μg , $p = 0.0014$; 1280 μg , $p = 0.041$). This improvement in FEV_1 was sustained during the 40-week open-label extension phase [58,59]. These data suggest that in the treatment of patients with moderate-to-severe asthma, ciclesonide provides significant improvements in FEV_1 and PEF compared with placebo in short- and long-term treatment. Longer-term studies are currently underway.

Active-comparator studies

Several studies have demonstrated that ciclesonide has comparable efficacy to two currently available ICS, fluticasone propionate and budesonide [20–22,61].

Clinical efficacy of ciclesonide versus fluticasone propionate

In one 12-week study of patients with asthma ($n = 529$), the efficacy of ciclesonide 160 μg once daily was compared with fluticasone propionate 88 μg twice daily (HFA-MDI, ex-actuator) [61]. Both ciclesonide 160 μg per day and fluticasone propionate 88 μg twice daily improved FEV_1 (506 ml and 536 ml, respectively) and morning PEF (29 l/min and 36 l/min, respectively) [61]. Ciclesonide was as effective as fluticasone propionate in improving FEV_1 and morning PEF ($p < 0.0001$ from baseline to week 12 in both groups) [61]. Similar improvements were also reported with FVC for both treatments (ciclesonide + 531 ml and fluticasone propionate + 523 ml). Compared with baseline, asthma symptoms were also significantly improved in both treatment groups at week 12 ($p < 0.0001$ for both) and the need for rescue medication was significantly reduced ($p < 0.0001$ for both) (Figure 3)[61].

Clinical efficacy of ciclesonide versus budesonide

There are also clinical data available suggesting that ciclesonide has comparable efficacy with budesonide. In a 12-week study, the efficacy and safety of two doses of ciclesonide 80 or 320 μg once daily were compared with budesonide 200 μg twice daily (Turbuhaler® ex-valve) in 554 patients with asthma [56]. In all treatment groups, FEV_1 and FVC increased significantly compared with baseline ($p < 0.0001$). Changes in FEV_1 % predicted were 9, 8 and 10% in

patients treated with ciclesonide 80 μg , ciclesonide 320 μg and budesonide 200 μg , respectively). In addition, both doses of ciclesonide were comparable to budesonide with respect to improvements in morning and evening PEF. The authors concluded that the once-daily dosing regimen of both doses of ciclesonide is as effective as budesonide 200 μg twice daily in patients with asthma [56].

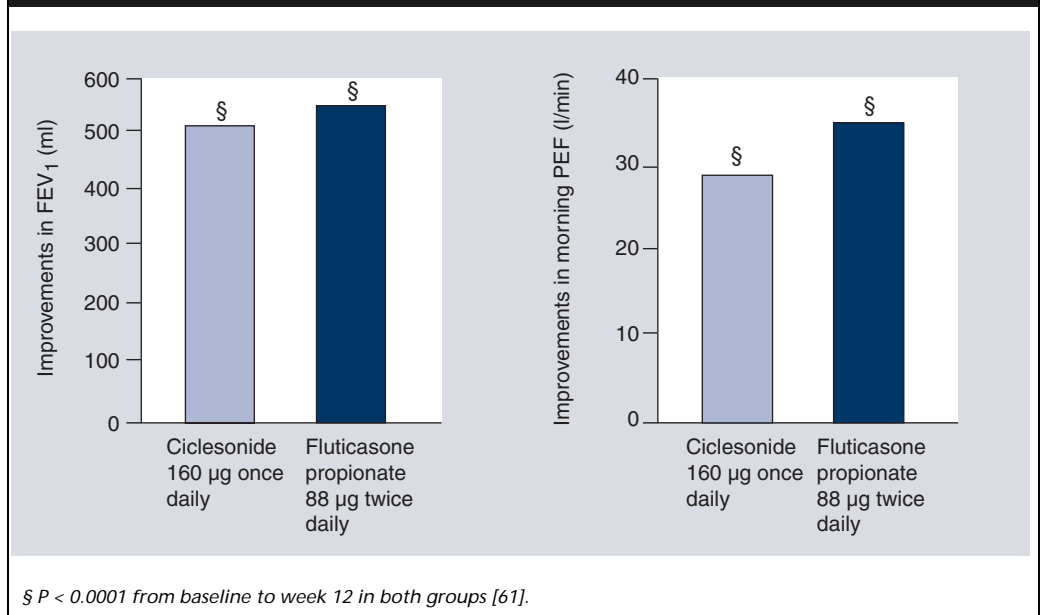
Two additional 12-week studies compared the effects of ciclesonide 320 μg once daily with budesonide 400 μg once daily (Turbuhaler ex-valve) on lung function in patients with asthma, and found ciclesonide to be at least as efficacious as budesonide [21,22]. The treatments were administered either in the morning [22] or the evening [21]. In the study in which the medications were administered in the evening ($n = 399$), treatment with ciclesonide 320 μg and budesonide 400 μg administered once daily significantly improved FEV_1 compared with baseline (411 ml and 319 ml, respectively, $p < 0.0001$). The superiority of ciclesonide versus budesonide was also demonstrated in FEV_1 ($p = 0.0374$). Daily recordings of morning PEF indicated an earlier onset of treatment effect for ciclesonide (day 3) compared with budesonide (week 2) [21].

In the second study, patients pretreated with beclomethasone dipropionate (400–800 μg per day) then received budesonide 1600 μg (Turbuhaler, ex-valve) per day for 2 to 4 weeks [22]. Patients who demonstrated a treatment response (defined as an improvement in FEV_1 of $\geq 7\%$ or 150 ml) and who had FEV_1 65–90% of predicted were then randomized to ciclesonide 320 μg via HFA-MDI ($n = 179$) or budesonide 400 μg ($n = 180$) once daily in the morning. At the end of 12 weeks of treatment, all patients experienced a decrease in FEV_1 and FVC. With ciclesonide, FEV_1 fell by 178 ml, compared with 232 ml for budesonide ($p = \text{NS}$ between groups). For FVC, there was less of a reduction with ciclesonide than with budesonide (124 ml versus 221 ml, respectively, $p < 0.01$). Patients receiving ciclesonide had a significantly higher percentage of symptom-free days compared with budesonide (43 versus 34%, $p = 0.0288$) [22]. The clinical benefits reported in these studies potentially could be attributed to differences in their pharmacologic profiles.

Clinical efficacy in the pediatric population

Clinical data from one comparative clinical trial illustrate that ciclesonide is also effective in children, compared with fluticasone propionate

Figure 3. Ciclesonide is as effective as fluticasone propionate in improving forced expiratory volume in one second (FEV₁) and morning peak expiratory flow (AM PEF) rate (n = 529).



[63]. In a multinational study, 556 children (aged 6 to 15 years) with persistent asthma were randomized to receive either ciclesonide 80 µg twice daily or fluticasone propionate 88 µg twice daily (via HFA-MDI, ex-actuator), for 12 weeks [63]. Ciclesonide was as effective as fluticasone propionate in improving all measured lung function parameters. During the 12-week treatment period, significant increases in FEV₁ were observed with both ciclesonide (298 ml) and fluticasone propionate (297 ml) ($p < 0.0001$ from baseline). In addition, asthma symptoms and the use of rescue medication were significantly reduced with both treatments compared with placebo ($p < 0.0001$) [63]. A number of ongoing short and long term studies are further evaluating the use of ciclesonide in the pediatric population.

Safety & tolerability

As has been noted previously in this paper, the potential for minimizing side effects is pivotal in the successful use of ICS treatment.

Local side effects

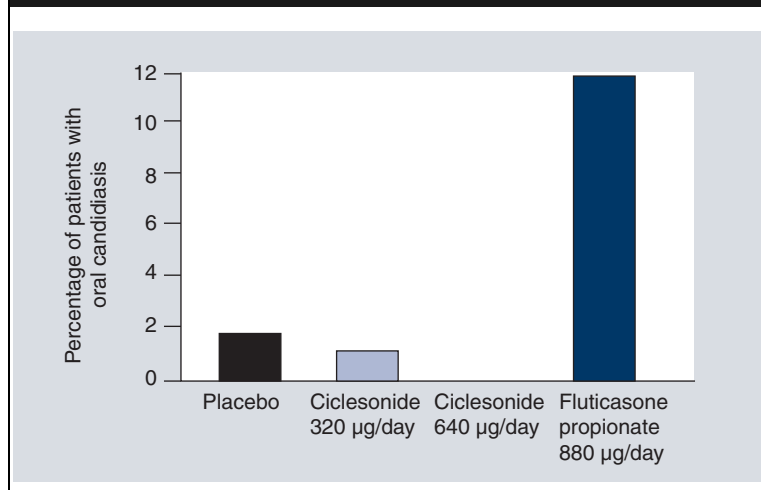
Ciclesonide 80 to 1280 µg daily is associated with a low frequency of local oropharyngeal adverse events [64–66]. Data pooled from a number of clinical studies, which included more than 6846 patients with asthma, demonstrated that the number of patients with oropharyngeal adverse events was similar in the ciclesonide and placebo groups [64]. In addition, a subset analysis

of this data highlighted that the incidence of oropharyngeal adverse events was lower in patients who received ciclesonide 640 µg (n = 465) compared with fluticasone propionate 880 µg (n = 483). The incidence of oral candidiasis was lower in patients receiving ciclesonide 640 µg daily compared with those receiving fluticasone propionate 880 µg (MDI, ex-actuator) (0.4% for ciclesonide 640 µg per day; 5.2% for fluticasone propionate 880 µg per day) [64]. Overall, a similar incidence of oropharyngeal adverse events was also reported in moderate-to-severe asthma patients taking ciclesonide 160 to 320 µg twice daily and fluticasone propionate 440 µg twice daily (chlorofluorocarbon MDI, ex-actuator) [27]. The incidence of oral candidiasis was higher in those patients who received fluticasone propionate 440 µg twice daily compared with those who received ciclesonide 160 or 320 µg twice daily (Figure 4) [27].

Local side effects in long-term studies

Longer-term clinical studies have also reported a low incidence of oropharyngeal adverse events with ciclesonide use [52,67]. For example, in one 52-week study, the incidence of oropharyngeal adverse events, including pharyngitis (4%), voice alteration (2%) and oral candidiasis (1%), was low in patients (n = 329) treated with ciclesonide 160 to 640 µg daily [52,67]. Ciclesonide has also been associated with a lower incidence of oral candidiasis than beclomethasone dipropionate

Figure 4. The incidence of oral candidiasis with ciclesonide was similar to placebo and less than for fluticasone propionate (n = 531) [27].



HFA-MDI (ex-actuator) [68]. In patients with severe, persistent asthma (n = 293), the incidence of oral candidiasis was lower in patients receiving ciclesonide 160 or 320 µg twice daily compared with beclomethasone dipropionate 160 or 320 µg twice daily for 52 weeks (4.1% for ciclesonide and 10.4% for beclomethasone dipropionate) [68].

Effects on HPA-axis function

The pharmacokinetic characteristics of ciclesonide, including low oral bioavailability, high serum protein binding and rapid systemic clearance, suggest that the agent may have a reduced potential to exert systemic side effects.

HPA-axis function in adults

Measures of HPA-axis function provide a sensitive clinical marker of the systemic exposure to an ICS [16]. In a clinical setting, integrated (area under the curve over 24 h [AUC₀₋₂₄]) serum or urinary free cortisol measurements, as well as dynamic stimulation of the HPA-axis with cosyntropin, are standard methods for assessing basal cortisol secretion and HPA-axis responsiveness, respectively [5].

In a healthy volunteer study, ciclesonide given as 640 µg once daily in the morning, 640 µg once daily in the evening or as 320 µg twice daily delivered via HFA-MDI for 7 days had no effect on the circadian rhythm of cortisol secretion compared with placebo as measured by 24 h AUC₀₋₂₄ serum cortisol [26].

The absence of HPA-axis suppression reported with ciclesonide in healthy volunteers was consistent with clinical findings in patients

with asthma. In an 8-week study, ciclesonide 160 µg daily had no effect on the HPA-axis, as determined by 24 h urinary free cortisol corrected for creatinine in patients with mild-to-moderate persistent asthma [10]. These findings were validated in a 40-week open-label extension (n = 228) of another 12-week study (n = 329), which showed that ciclesonide (160–1280 µg daily) did not suppress 24 h urinary cortisol levels [52,67].

Several pharmacodynamic studies have provided further evidence that ciclesonide does not adversely affect HPA-axis function [20,25,69]. In repeat-dose studies in asthma patients, ciclesonide 320 to 1280 µg per day and placebo had similar effects on the HPA-axis, as assessed by such measures as AUC₀₋₂₄ serum cortisol levels, urinary free cortisol corrected for creatinine levels and dynamic peak serum cortisol concentrations after stimulation with 1 µg cosyntropin [20,25,69].

Studies have also provided evidence suggesting that ciclesonide may have less effect on HPA-axis suppression than other ICS [56,70]. For example, a 12-week study in patients with mild-to-moderate asthma showed that ciclesonide 80 or 320 µg once daily was not associated with changes in 24 h urinary cortisol excretion compared with baseline. Conversely, treatment with budesonide 200 µg twice daily (Turbuhaler ex-valve) showed statistically significant suppression (p < 0.05) [56]. These results have also been found with higher doses of ciclesonide. For example, a 4-week study of patients with moderate, persistent asthma showed that treatment with fluticasone propionate 880 µg twice daily (ex-actuator) suppressed HPA-axis function, whereas ciclesonide 640 µg twice daily had no such effect [70].

HPA-axis function in the pediatric population

HPA-axis suppression and growth impairment are of particular concern in pediatric patients. The systemic safety of ciclesonide has been investigated in 556 children with persistent asthma aged 6 to 15 years receiving ciclesonide 160 µg daily (80 µg twice daily) in a randomized 12-week comparison study with fluticasone propionate 176 µg daily (88 µg twice daily; HFA-MDI, ex-actuator) [63]. There were no statistically significant between treatments differences in urinary cortisol excretion. Similarly, a double-blind, placebo-controlled, four-period cross-over study of 24 children with mild, persistent asthma found no clinically relevant difference in

urinary free cortisol (creatinine-corrected) in patients treated with ciclesonide 40, 80 or 160 µg once daily or placebo [71]. Combined data from two 12-week placebo-controlled studies of children aged 4 to 11 years with mild-to-severe persistent asthma illustrated that ciclesonide (40, 80 and 160 µg once daily) treatment did not suppress HPA-axis function as measured by peak serum cortisol concentrations after stimulation with 1 µg cosyntropin and 24 h cortisol corrected for creatinine [72].

Impairment of growth

One consequence associated with systemic exposure to ICS therapy may be growth impairment in children [73]. Indeed the results of one placebo-controlled, four-period cross-over study in children with mild, persistent asthma (n = 24) demonstrated that ciclesonide 40 to 160 µg once daily did not affect lower-leg growth rate [71]. The growth rate of the lower leg was approximately 0.4 mm/week in each treatment group, with no statistically significant differences between any ciclesonide treatments and placebo. The authors concluded that ciclesonide 40 to 160 µg once daily has a favorable safety profile for use in children.

HPA-axis suppression in long-term studies

The lack of effect of ciclesonide on HPA-axis function was recently demonstrated in a long-term study in patients aged 12 years or over with severe, persistent asthma [74]. In a 12-month double-blind, parallel group extension of a 12-week, double-blind, randomized study, ciclesonide 160 or 320 µg twice daily had similar effects to beclomethasone dipropionate 160 or 320 µg twice daily (both delivered via HFA-MDI, ex-actuator) on HPA-axis function. Mean changes from baseline to study end in low-dose cosyntropin peak serum cortisol levels and 24 h urinary free cortisol corrected for creatinine values were comparable between the treatment groups [74]. Other ongoing studies are evaluating the effect of long-term exposure to inhaled ciclesonide on other organs and body systems, including growth in children, which may be affected by chronic exposure to ICS therapy.

Expert opinion

The role of ICS therapy in the treatment of asthma is well established – ICS are proven efficacious and are recommended as first-line therapy for individuals with persistent asthma. Despite

their benefits, however, all of the commercially available ICS are associated with some undesirable systemic and local side effects, including oropharyngeal adverse effects. Concerns relating to ICS safety may affect usage, especially in the pediatric population, which may result in suboptimal asthma control. This may lead to an unnecessary increase in asthma exacerbations, while reducing patient quality of life as it relates to missing time at school and activities such as sports. Such lifestyle limitations are of particular concern among the pediatric population. Clearly there is a need for an ICS that provides effective asthma control, with a reduced potential for local and systemic side effects, to ensure efficacy and appropriate adherence. Ciclesonide, with its improved therapeutic margin, has the potential to offer this option, in providing efficacy similar to that of other ICS, with an improved safety profile.

The beneficial treatment effects associated with ciclesonide may be linked to its pharmacokinetic and pharmacodynamic properties. Ciclesonide is a parent compound that is converted primarily in the lung to an active metabolite, des-ciclesonide. Des-ciclesonide displays a high receptor affinity and the ability to form reversible lipid conjugates. A potentially prolonged pulmonary retention time may further enhance the efficacy of ciclesonide, which may allow for a once-daily dosing regimen in adults and children with mild-to-moderate persistent asthma.

In addition to improving efficacy, ciclesonide has pharmacokinetic characteristics that may lead to an improved safety profile as well. For example, ciclesonide has a reduced potential for local oropharyngeal adverse effects, due to the relatively low deposition of ciclesonide in the oropharynx and minimal conversion to active ICS. Furthermore, the small fraction of ciclesonide that becomes systemically available is rapidly cleared and highly protein bound, which reduces the likelihood of systemic side effects.

Outlook

ICSs are considered the cornerstone of therapy for the long-term control of asthma, and as such, it is essential that efforts be made to improve the safety profile and patient acceptance of this class of agent that is so critical for the treatment of asthma. It has been proposed that the 'ideal' ICS may improve treatment adherence to provide long-term control of this disease. The developmental program of ciclesonide is ongoing and further studies will be conducted. Currently available data suggest that ciclesonide is a step closer to an

Highlights

- Inhaled corticosteroids (ICSs) are recommended as first-line therapy for individuals with persistent asthma of all severities and adherence to therapy is necessary to maintain long-term control of this disease. However, factors such as dosing frequency, the delivery device and safety concerns impact patient adherence. Therefore, an effective ICS that allows for a once-daily dosing schedule with a reduced potential for local and systemic side effects may ultimately improve the long-term management of this disease.
- Ciclesonide is a novel ICS with potent anti-inflammatory properties currently under development for the treatment of mild-to-severe persistent asthma.
- Ciclesonide is formulated as a solution for delivery via a hydrofluoroalkane metered-dose inhaler which results in a high lung deposition. Importantly, the parent compound ciclesonide is inactive until it is converted to the active compound desisobutyryl-ciclesonide in the target tissues, which, together with its pharmacologic properties, contribute to the improved therapeutic margin of this drug.
- Ciclesonide has demonstrated efficacy comparable to that of other ICSs in patients with persistent asthma, but with minimal local or systemic side effects.
- Ciclesonide has the potential for a once-daily dosing regimen in adults with mild-to-moderate asthma and children with all severities of the disease, which may improve adherence and ultimately, long-term asthma control.

‘ideal’ ICS, which may provide effective asthma control with a reduced propensity for systemic and local side effects.

Information resources

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