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REVIEW

Profile of ciclesonide for the maintenance treatment of asthma

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Effie Singas[1,2]
Jill P Karpel[3,4]

[1]North Shore University Hospital, NS-LIJ Health System, [2]Hofstra North Shore – LIJ School of Medicine, [3]North Shore Medical Arts, [4]Albert Einstein College of Medicine, New York, NY, USA

Abstract: Ciclesonide is a nonhalogenated synthetic inhaled corticosteroid (ICS) that has been approved by the US Food and Drug Administration for the treatment of all severities of persistent asthma. It is available as a hydrofluroalkane pressurized metered-dose inhaler in two strengths, 80 mcg/activation and 160 mcg/activation, with the recommenced dosage being two inhalations twice-daily. It is a prodrug that is converted in the lung to its active form, which possesses 100-fold greater glucocorticoid-receptor-binding affinity than the parent compound. Its relative receptor affinity is similar to budesonide. In clinical studies, ciclesonide was effective in improving pulmonary function, reducing asthma symptoms, and reducing or eliminating the need for oral corticosteroids (OCSs). Patients with severe asthma dependent on OCSs and high doses of ICSs were able to achieve greater asthma control and reduce or even eliminate the use of OCSs when switched to ciclesonide. In comparison with fluticasone propionate and budesonide, ciclesonide was demonstrated to be at least as effective in maintaining pulmonary function and asthma control. In clinical trials, ciclesonide was well tolerated, with the majority of adverse events considered mild or moderate in intensity. It had low systemic bioavailability and no clinically significant hypothalamic–pituitary–adrenal axis suppression at therapeutic doses. Its safety profile establishes ciclesonide as an important addition to the currently available ICSs.

Keywords: ciclesonide, asthma, maintenance, corticosteroids

Introduction

Asthma is a chronic inflammatory disease of the airways that results in airway obstruction that is thought to be largely reversible. It is characterized by recurrent episodes of wheezing, dyspnea, chest tightness, and coughing. There is a significant health burden associated with asthma due to its resultant morbidity, mortality, and cost.

Both national and international guidelines have been developed to improve the diagnosis, management, and outcomes of asthma.[1,2] For all categories of persistent asthma, inhaled corticosteroids (ICSs) are the cornerstone or first-line therapy due to their potent anti-inflammatory properties, which primarily result in reduced numbers of airway inflammatory cells and their subsequent mediators. Clinically, they reduce bronchial hyperreactivity, asthma symptoms, exacerbations, urgent care visits, and hospitalizations, while improving lung function and quality of life.

Current guideline recommendations are to treat mild asthma with a low-dose ICS, while moderate asthma (patients ≥12 years) may be treated with either a medium-dose ICS or a low-dose ICS with the addition of a long-acting-beta-2-agonist (LABA).[1] For severe persistent asthma patients, combination therapy with a medium- to high-dose ICS plus a LABA is recommended, possibly with the addition of omalizumab or oral

Correspondence: Effie Singas
410 Lakeville Road, Suite 107,
New Hyde Park, NY 11040, USA
Tel +1 516 465 5400
Fax +1 516 465 5454
Email esingas@nshs.edu

corticosteroids (OCS) if control is not achieved. However, it is also a guideline recommendation that once control is achieved for a period of time (ie, at least 3 months), the ICS dose should be titrated downward to the lowest dose possible to maintain control. This is to hopefully minimize any systemic absorption that might result in potentially adverse effects such as hypothalamic–pituitary–adrenal axis (HPA axis) suppression, growth retardation in children, decreased bone mineral density, cataracts, skin thinning, and easy bruising. ICSs are usually well tolerated and considered to be safe at the recommended doses. The occurrences of adverse effects are considered to be related to both the dose administered and the duration of treatment. When treating patients with asthma, the risk/benefit of each treatment step (up or down) should be weighed against the outcomes associated with uncontrolled asthma.

In keeping with the above philosophy, newer ICSs are being developed to address the needs unmet by current ICS therapy. Some of the goals in the development of new ICSs would be to: improve therapeutic indexes, particularly at higher dosages; have less frequent dosing intervals to encourage patient adherence; and maintain clinical effectiveness and potency.

Ciclesonide (CIC) is indicated for the treatment of persistent asthma in patients aged 12 years or older. It is available in a hydrofluroalkane pressurized metered-dose inhaler (HFA-MDI) in two strengths, 80 mcg/actuation and 160 mcg/actuation, administered twice-daily. The recommended starting dose for patients receiving as-needed inhaled bronchodilators alone is CIC 80 mcg twice-daily with a maximum dose of 160 mcg twice-daily. For patients receiving inhaled steroids, the starting dose is 80 mcg twice-daily to a maximum dose of 320 mcg twice-daily. For patients receiving oral corticosteroids, it is recommended that patients start at the maximal dose of 320 mcg twice-daily with taper of oral prednisone no faster than 2.5 mg/day on a weekly basis, starting at least 1 week after initiation of CIC therapy.[3]

Pharmacologic features of ciclesonide

Pharmacokinetics

CIC is a nonhalogenated ICS that is available as a HFA-MDI in two strengths, 80 mcg/actuation and 160 mcg/actuation, and it is administered twice-daily. Like beclomethasone dipropionate, it is a prodrug that is converted to its active form desisobutyryl-ciclesonide (des-CIC) via esterases in the lung, maximizing its local effects. The parent compound CIC is inactive with a relatively low glucocorticoid-receptor affinity (RRA) of 12. Des-CIC has a 100-fold greater relative-glucocorticoid-receptor-binding affinity than CIC (RRA = 1200). The potency of an ICS is assessed in terms of its relative receptor affinity versus dexamethasone, which is assigned a value of 100.[4] An ICS with a higher RRA will induce a greater anti-inflammatory effect. In comparison with other available ICSs, des-CIC's RRA is between that of mometasone fuorate (MF) (which has a RRA of 2300), fluticasone propionate (FP) (RRA: 1800), and budesonide (BUD) (RRA: 935), and it is similar to beclomethasone monopropionate (17-BMP) (RRA: 1345).[5] Increasing the potency of a glucocorticoid leads to higher topical efficacy but also may lead to more systemic activity and a higher incidence of systemic side effects, as the glucocorticoid receptor is expressed in almost all tissues and cells.[5]

ICSs are deposited in the upper airway and the lungs. Depending on the formulation and inhaler device, a large portion of the drug may be deposited in the oropharynx, swallowed, and then absorbed systemically where it can contribute to potential adverse effects. It is desirable for the oral bioavailability of ICSs to be low so that the drug has low systemic absorption from the gastrointestinal tract and for there to be extensive first-pass metabolism so that the amount of drug that is absorbed is rapidly cleared, minimizing systemic effects. CIC has been formulated as a solution HFA-MDI, with particles ranging 1.1–2.1 μm, small enough to deposit in the small distal airways, which average 2 μm in size.[4] In two studies, one involving healthy subjects and a second study involving patients with mild asthma, technetium labeled CIC was shown to reach all regions of the lung with higher deposition in the peripheral regions than in the central region, and higher deposition in the whole lung than in the oropharynx.[6,7] The inhaled bioavailability of des-CIC is 52% compared with 17% for FP via DPI, 29% for FP via HFA-MDI, 68% for FLU via HFA-MDI, 55%–60% for beclomethasone (BDP) via HFA-MDI, and 11% for MF.[5]

CIC also exhibits low oropharyngeal deposition and low activation to des-CIC in the oropharynx.[4] Any drug that reaches the systemic circulation binds to plasma proteins such as albumin and transcortin. Only the free, unbound drug is pharmacologically active and capable of suppressing endogenous cortisol. If the drug freely dissociates, this is not an issue. CIC has the highest degree of protein binding (99%) followed by MF (98%–99%), 17-BMP (98.4%) and FP (90%).[5]

Since there is low oropharyngeal deposition of CIC, low activation to des-CIC, and high protein binding,

the potential for local and systemic side effects is low. Furthermore, any absorbed drug is subjected to nearly complete first-pass metabolism. This was demonstrated in a study where healthy subjects were given orally a single dose of 6.9 mg of labeled CIC and intravenously 0.64 mg, and radioactivity was determined in blood, plasma, urine, and feces. Total radioactivity in the systemic circulation was low, and CIC was not detected in any serum sample. Serum concentrations of des-CIC were near or below the lower limit of quantification, giving a systemic bioavailability of <1% for des-CIC.[8] Elimination occurred mostly via the feces and was complete by 120 hours after both oral and IV administration. Following intravenous administration of 800 mcg of CIC, the clearances of CIC and des-ciclesonide were high (approximately 152 L/h and 228 L/h, respectively).[3] ^{14}C-labeled CIC was predominantly excreted in the feces after intravenous administration (66%), indicating that excretion through bile is the major route of elimination. Approximately 20% or less of des-CIC was excreted in the urine. The mean half-life of CIC and des-CIC was 0.71 hours and 6–7 hours, respectively. T_{max} of des-CIC occurs at 1.04 hours following inhalation of CIC.[3]

CIC has several favorable properties, including its prodrug structure, high-lipid affinity and glucocorticoid receptor-binding affinity of the active drug des-CIC, low oral deposition and bioavailability, extensive peripheral distribution in the lung, high protein-binding, and extensive first-pass metabolism. These properties may lead to a higher therapeutic efficacy and lower systemic exposure, thereby minimizing potential systemic effects.

Pharmacodynamics

CIC has been shown to have anti-inflammatory effects in vitro, with des-CIC conferring even greater anti-inflammatory activity. CIC and/or des-CIC were effective in inhibiting proinflammatory functions, including the stimulated expression of intracellular adhesion molecule-1, and stimulated release of inflammatory mediators such as granulocyte-macrophage colony-stimulating factor, monocyte chemoattractant protein (MCP)-1, interferon-gamma, interleukin (IL)-2, IL-4, IL-5, IL-8, and tumor necrosis factor (TNF)-a. CIC and des-CIC inhibited the induced proliferation of immune cells such as peripheral blood mononuclear cells, CD4 lymphocytes, and human airway smooth muscle cells.[9–11]

In a small trial of patients with mild persistent asthma, once-daily CIC 320 mcg significantly ($P < 0.05$ versus placebo) inhibited levels of IL-12 and MCP-1 in sputum within 4 hours of administration. Inhibition of IL-12, MCP-1, IL1a, IL-6, IL-7, and IL-8 in sputum was observed within 4 hours of twice-daily administration of CIC 640 mcg versus placebo ($P < 0.01$). After 1 week of treatment with twice-daily CIC 640 mcg, interferon (INF)-inducible protein 10 was significantly ($P < 0.001$) inhibited compared with placebo.[12]

Once-daily CIC 80 mcg attenuated allergen-induced increases in the production of IL-4 and IL-5 in patients with mild atopic asthma. The drug also reduced chemokine-induced T-cell migration versus placebo prior to and 6 hours after allergen challenge.[13]

Several studies have shown that treatment with CIC reduced the percentage of eosinophils in induced sputum of patients with asthma. CIC (40 and 80 mcg/day) attenuated the number of eosinophils in the sputum 8 hours but not 24 hours after allergen challenge.[14] In another study, sputum eosinophilia was significantly attenuated with CIC 40 and 80 mcg/day 24 hours after allergen challenge.[15]

Effect on eosinophil-cationic-protein release was not as consistent, with two studies[16,17] showing reduction from pretreatment levels with CIC 400 mcg/day; however, no effect was seen with CIC 100 and 1600 mcg in the one study.[16] In another study, CIC 40 mcg/day was found to attenuate allergen-induced reduction in IFN-γ-positive-CD4 T-cells 24 hours after provocation, although this effect was not seen with CIC 80 mcg/day.[14]

CIC also reduced levels of exhaled nitric oxide (NO) in patients with mild to moderate asthma. In a randomized double-blind, placebo-controlled, randomized crossover, study of 17 patients, exhaled NO levels were measured after treatment with CIC 160 mcg once-daily for 4 weeks. Exhaled NO difference between CIC and placebo was 47 ppb (95% confidence interval [CI]: 15–81 ppb).[18] A preliminary study suggested CIC produced a greater and more rapid reduction in exhaled NO than comparable doses of fluticasone.[19]

In summary, CIC has significant anti-inflammatory effects, which support its clinical efficacy in the studies that follow.

Clinical efficacy and safety studies

Ciclesonide versus placebo

A 2008 Cochrane review evaluated randomized parallel or crossover studies comparing CIC at different doses with placebo.[20] Eighteen trials, which included 6343 participants, of which 1692 were children, met the review entry criteria.

At doses of ≤100–400 mcg/day in mild to moderate asthma, CIC improved lung function, asthma symptoms, and rescue inhaler use, compared with placebo. Comparisons of CIC at different doses did not yield significant differences in lung function. The short duration of these trials precluded conclusions regarding the effectiveness of CIC in preventing asthma exacerbations.

Table 1 summarizes the key findings in a representative sample of trials comparing the efficacy and safety of CIC at different doses with placebo.

The US Food and Drug Administration recommended dosing was based on review of the above studies. The trial by Berger et al specifically demonstrated that CIC in a twice-daily dosing regimen was superior at improving pulmonary function and controlling disease symptoms than the CIC at twice the dose on a once-daily dosing regimen and was superior to placebo.[25] This trial supported the presence of a dose frequency–dependent effect of the ICS on lung function and led to approval only for BID dosing in the USA.

Bateman et al investigated the effectiveness of CIC to reduce oral corticosteroid use in patients with severe, persistent asthma who were steroid dependent.[26] Patients received CIC delivered via HFA-MDI at 320 mcg twice-daily, CIC delivered via HFA-MDI at 640 mcg twice-daily, or placebo (all received at 8 am and 8 pm). At study end, CIC 640 mcg/day and CIC 1280 mcg/day significantly reduced prednisone use whereas steroid use increased in the placebo group. Furthermore, 30% of patients in the CIC groups were able to discontinue prednisone entirely and significantly fewer patients in the CIC groups required an increase in prednisone dose compared with placebo. These results suggest that CIC significantly reduces the need for oral corticosteroids in patients with severe, persistent asthma and maintains asthma control.

In summary, CIC has been demonstrated to be an effective ICS for patients with mild, moderate, and severe persistent asthma. Additionally, it can be beneficial in reducing oral corticosteroid requirements in OCS-dependent asthma patients.

Comparisons with other inhaled corticosteroids

A 2009 Cochrane review assessed the efficacy and adverse effects of CIC compared with those of other ICSs in the management of chronic asthma.[27] Randomized parallel or crossover studies were reviewed. Studies comparing CIC with other steroids both at nominally equivalent dose or lower doses of CIC were included. Twenty-one trials involving 7243 participants (children and adults) were included. Equivalent daily doses of CIC and beclomethasone diproprionate (BDP) or BUD demonstrated similar results for peak expiratory flow rates. However, forced vital capacity (FVC) was higher with CIC, while forced expiratory volume (FEV_1) data were inconsistent. When CIC was compared with equivalent doses of FP, FEV_1, FVC, and peak expiratory

Table 1 A representative sample of trials evaluating the efficacy of ciclesonide (CIC) in the treatment of asthma in adults and adolescents

Trial	Study design (n of patients)	Pulmonary function	Asthma symptom score	Rescue medication use
Chapman et al[21]	12 wk, DB, R, PG, PC, 329 pts, CIC 160, CIC 640, vs PL	PEF and FEV_1 did not change with either CIC dose[a], decreased with PL	Worsened with PL, stable with either CIC[a] dose	Increased in PL vs both CIC groups[a,b]
Adachi et al[22]	8 wk, PC, DB, PG, CIC 80 (78), CIC 160 (71), CIC 320 (83), vs PL (79)	PEF did not change with any CIC dose, decreased with PL[a]	Worsened with PL, stable with all CIC doses	Decreased in all CIC groups vs PL
Langdon et al[23]	12 wk, R, PC, CIC 80 (120), 320 (115), vs PL (125)	PEF maintained in CIC groups, decreased in PL[a] FEV_1 increased in CIC groups,[a,c] slight decrease in PL ($P = 0.54$)	Worsened with PL, stable with all CIC doses[a]	Stable in CIC groups, increased in PL
Pearlman et al[24]	12 wk, MC, DB, R, PG, PC, CIC 80 (257), CIC 160 (250), CIC 320 (255), PL (249)	FEV_1 and PEF improved in all CIC groups vs PL	Improved with all CIC groups vs PL	Reduced in CIC groups, increased in PL
Berger et al[25]	16 wk, MC, MN, DB, PG, PC, R, CIC 80 BID (170), CIC 160 QD (173), CIC 80 BID/CIC 160 QD (171) PL (177)	FEV_1 improved in all CIC groups, greatest improvement in CIC 80 BID. AM PEF improved in all CIC groups[a] vs PL	Improved in all Rx groups, CIC 80 groups improved vs PL	Decreased in all treatment groups, greatest reduction in CIC groups

Abbreviations: DB, double blind; R, randomized; PG, parallel group; PC, placebo controlled; MC, multicenter; MN, multinational; AM, morning; PL, placebo; wk, week.
Notes: [a]No significant difference between CIC groups; [b]no change from baseline; [c]versus baseline; only statistically significant differences are reported to $P < 0.05$, unless otherwise noted; all reported doses are exactuator and in micrograms; all medication was delivered via hydrofluoroalkane metered dose inhaler; there were no significant adverse events noted in any of the studies.

flow (PEF) did not differ significantly. Candidiasis was less frequent with CIC, although there were no significant differences in other side effects. When lower doses of CIC were compared with BDP or BUD, the difference in FEV_1 did not reach significance. Other lung function outcomes did not demonstrate significant differences between treatments. Adverse events occurred with similar frequency between CIC and BDP/BUD. In three studies, CIC was compared with FP at half the nominal dose and FEV_1 was not significantly different but was also not equivalent between the treatments (per protocol: –0.05 L, 95% CI –0.11–0.01).

Table 2 reviews the key findings in a representative sample of trials comparing CIC to FP and BUD in adults and adolescents with mild, moderate, and severe persistent asthma. Of note, the majority of adverse events (AEs) were assessed as unrelated to study medication and were mild to moderate in intensity. No significant lab abnormalities were noted. In the Buhl et al[28] study, three patients receiving FP developed oral AEs, including voice alteration or oral candidiasis. In the Boulet et al[30] and Bateman et al[31] studies, significantly more patients treated with FP developed local oral AEs. Hansel et al[33] noted a significant decrease in urinary cortisol concentration in patients

Table 2 A representative sample of trials comparing the efficacy and safety of ciclesonide (CIC) to other inhaled corticosteroids

Trial	Study design (number of patients)	Pulmonary function	Asthma symptom score	Rescue medication use
Buhl et al[28]	12 wk, MC, R, DB, DD, PG study CIC 160 qd (266)[b] vs FP 88 BID (263)[b]	PEF and FEV_1 improved significantly in both groups[a]	Improved in both treatment groups	Not different between treatment groups
Magnussen et al[29]	12 wk, DB, DD, PG, R, CIC 80 qd (278)[b], CIC 160 qd (271)[b] or FP 88 BID (259)[b]	FEV_1 improved significantly in all Rx groups[a] Site measured PEF improved significantly in all Rx groups	Improved in all treatment groups[a]	Decreased to similar extent in all treatment groups[a]
Boulet et al[30]	12 wk, R, OL, PG, CIC 320 qd (234)[b], FP 200 BID (240)[c]	FEV_1 improved significantly in both Rx groups[a] AM PEF improved significantly in CIC group	Improved in both groups[a]	Decreased in both treatment groups[a]
Bateman et al[31]	24 wk, R, MC, OL, PG, CIC 320 BID (255)[b], FP 330 BID (273)[b]	FEV_1 maintained in both Rx groups[g] PEF improved significantly in both Rx groups[a]	Improved in both Rx groups[a]	Decreased in both Rx groups
Niphadkar et al[32]	12 wk, R, MC, PG, DB, DD, of CIC with OL BUD BID, CIC 160 QAM (139)[b], CIC 160 QPM (131)[b] or BUD 200 BID (133)[b]	FEV_1 maintained in all Rx groups[a] No significant differences found among Rx groups for PEF	Maintained in all Rx groups[a]	Maintained in all Rx groups vs baseline[a]
Hansel et al[33]	12 wk, MC, R, DB for CIC, OL for BUD, of CIC 80 qd (182)[b], CIC 320 qd (195)[b] vs BUD 200 BID (177)[f]	FEV_1 improved in all groups at 12 wks. No significant difference between CIC groups. PEF improved in all groups[a]	Improved in all Rx groups	Decreased in all groups
Boulet et al[34]	12 wk MC, R, DB, DD, PG study, CIC 320 qd (179)[b], vs BUD 320 qd (180)[d]	Change in FEV_1 was similar in both Rx groups. Mean PEF did not change in either Rx group	No significant difference in scores between Rx groups	Decreased in CIC group
Ukena et al[35]	12 wk DB, DD, R, PG study, CIC 320 qd (198)[b] vs BUD 400 qd (201)[d]	FEV_1 improved in both Rx groups, CIC demonstrating superiority over BUD. PEF improved in both Rx groups, CIC showed greater increase than BUD	Improved in both Rx groups[a]	Decreased in both Rx groups[a]
Vermeulen et al[36]	12 wk MC, R, DB, DD, PG, CIC 320 qd[b] (272) vs BUD 800 qd (131)[d]	FEV_1 increased in both Rx groups.[a] AM and PM PEF increased significantly only in CIC group.	Improved in both Rx groups[a]	Decreased in both Rx groups

Notes: Only statistically significant differences are reported to $P < 0.05$, unless otherwise noted; all reported doses are ex-actuator and in micrograms; [a]no statistically significant difference noted between the treatment groups; [b]delivered via HFA-M; [c]delivered dry powder via inhaler (diskus); [d]delivered via Turbohaler; [f]delivered via dry powder inhaler; [g]no significant change seen from baseline to study end.

Abbreviations: AM, morning; DB, double blind; DD, double dummy; R, randomized; PG, parallel group; PC, placebo controlled; MC, multicenter; OL, open label; CIC, Ciclesonide; FP, Fluticasone propionate; BUD, Budesonide; AE, adverse event; wk, week; Rx, treatment; qd, once-daily; BID, twice-daily; vs, versus; QAM, every morning; QPM, every evening; PEF, peak expiratory flow; FEV_1, forced expired volume in one second.

receiving BUD. Ukena et al[35] noted four AEs (cough, headache, dyspnea, and voice alteration) potentially related to CIC.

Effect of ciclesonide on HPA axis

Dose-related adverse effects have been described for ICSs, especially in patients with moderate-to-severe asthma who may require higher doses to achieve asthma control. Systemic adverse effects that have been reported include osteoporosis, growth suppression, cataracts, glaucoma, and adrenal insufficiency, while local adverse effects include hoarseness, dysphonia, pharyngitis, and oral candidasis.

HPA axis

Lipworth evaluated the potential effects of CIC therapy on the dynamic cortisol response to sequential low- and high-dose cosyntropin stimulation in adults with mild-to-moderate persistent asthma.[37] In a double-blind, placebo-controlled, 12-week study, 164 patients were randomized to placebo, 320 mcg CIC once-daily, 320 mcg CIC twice-daily (all CIC doses delivered via HFA-MDI), and 440 mcg FP twice-daily delivered via CFC-MDI, all doses ex-actuator. Patients had normal HPA-axis function at screening and had not used systemic corticosteroids within 6 months of screening or inhaled or intranasal corticosteroids within 2 months of screening.

CIC at doses up to 640 mcg/day does not affect sensitive markers of adrenal function. CIC did not produce any significant suppression of either basal cortisol levels or the response to cosyntropin stimulation, with results almost identical to the placebo group. In contrast, the FP group showed significant suppression of 24-hour-urinary-free cortisol levels and on high-dose cosyntropin stimulation compared to the placebo group. The differences between CIC groups and FP were statistically significant. Thus, CIC may result in less adrenal suppression than FP.

Local effects

Oral candidasis occurred in 22.0% of FP group compared with 2.4% in the combined CIC groups. Hoarseness occurred at a rate of 7.3% in the FP group and 2.4% in the combined CIC groups.[37]

Systemic effects

Other potential systemic effects of inhaled corticosteroids include decreased bone mineral density, cataract formation, glaucoma, and growth suppression.

Derom looked at markers of bone metabolism in a randomized, double-blind, double-dummy, placebo-controlled, five-period crossover study conducted at two centers.[38] CIC 160, CIC 320 BID, FP 250 BID, FP 500 BID, or placebo were compared, which were administered in addition to a maintenance dose of CIC 160 qd. No significant differences were noted after any CIC treatment compared with placebo for any bone formation marker, which included N-terminal propeptide of type 1 procollagen (P1NP), alkaline phosphatase (AP), and serum osteocalcin. FP 1000 caused significant decreases in P1NP ($P = 0.0126$) and serum osteocalcin levels ($P = 0.0054$) compared with placebo. The clinical significance of these findings is not clear.

Chylack demonstrated that treatment with CIC 640 mcg/day or beclomethasone dipropionate 640 mcg/day for 1 year had a minimal impact on lenticular opacity development and/or progression.[39]

A 52-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group study was conducted to assess the effect of CIC on growth rate in 609 pediatric patients aged 5–8.5 years. Patients were randomized to CIC 40 mcg, 160 mcg, or placebo once-daily. Growth was measured during baseline, treatment, and follow-up periods. There was no difference in efficacy measures, but conclusive results could not be drawn because compliance could not be assured.[3]

These studies suggest that CIC has minimal systemic adverse effects.

Conclusion

CIC is a nonhalogenated ICS, available as a HFA-MDI in two strengths, 80 mcg/actuation and 160 mcg/actuation, administered twice-daily. Several properties, including its prodrug structure, high lipid affinity, and glucocorticoid receptor–binding affinity of the active drug des-CIC, low oral deposition, low oral bioavailability, extensive peripheral distribution in the lung, high protein binding, and extensive first-pass metabolism, favor higher therapeutic efficacy and limited systemic exposure. CIC has significant anti-inflammatory effects that also contribute to its clinical efficacy. Studies have shown that CIC improves lung function, asthma symptoms, and rescue inhaler use, compared with placebo in patients with mild, moderate, and severe persistent asthma. CIC also significantly reduces the need for oral corticosteroids in patients with severe persistent asthma and maintains asthma control. CIC is at least as effective as FP, BUD, and beclomethasone propionate in maintaining pulmonary function, asthma control, and improving symptoms. Most significantly, CIC at doses up to 640 mcg/day does not suppress either basal cortisol levels or the response to cosyntropin stimulation. CIC may

cause less adrenal suppression than FP. Studies evaluating growth rate, lens opacity development, and markers of bone metabolism suggest that CIC's systemic effects are minimal. The unique contribution of CIC in the treatment of asthma lies in its excellent safety profile.

Disclosure

ES has no conflicts of interest to disclose in relation to this paper. JK discloses the following conflicts of interest:

- Current research: Forest Labs, Boerhingher-Ingelheim, Novartis, Genentech.
- Speaker's bureaus: Genentech, Novartis, Astra-Zenecca, Merck, Boehringher-Ingelhiem.

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