

Original Article

Ciclesonide Impacts Clinicopathological Features of Eosinophilic Esophagitis

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What is already known about this topic? Ciclesonide is a topical steroid that was developed to increase local bioavailability in the lung and reduce systemic exposure. Limited reports identify its use in patients with eosinophilic esophagitis.

What does the article add to our knowledge? In 81 patients ranging in age from 2 to 23 years, ciclesonide reduced symptoms, improved esophageal endoscopic appearance, and decreased epithelial inflammation without any severe side effects.

How does this study impact current management guidelines? Ciclesonide provides effective treatment for eosinophilic esophagitis with limited systemic exposure, thus potentially reducing the risk of adrenal suppression.

BACKGROUND: Eosinophilic esophagitis (EoE) is a chronic allergen-mediated disease of the esophagus. Pharmacologic treatment has largely relied on repurposing corticosteroids. Ciclesonide (CIC) is a corticosteroid for the treatment of asthma with biochemical properties that improve topical potency.

OBJECTIVE: To determine whether CIC decreased clinicopathological features of EoE.

METHODS: We performed a retrospective cohort study of patients with EoE treated with CIC at a pediatric hospital from 2010 to 2019. Data were extracted from the electronic health record. Patients who were prescribed CIC with pre- and post-CIC endoscopic and histological data available were included for analysis.

RESULTS: A total of 281 patients were treated with CIC and 81 met criteria for inclusion. Use of CIC was associated with reduced symptoms including dysphagia ($P < .001$), abdominal pain ($P < .001$), vomiting ($P = .01$), heartburn ($P = .02$), and behavior changes ($P = .02$). Average composite endoscopic reference scores decreased from 2.54 to 1.37 ($P < .001$), with improvement in exudates, edema, and furrows (all $P < .001$). Peak eosinophil counts decreased from 48 to 23 eosinophils/hpf

($P < .001$). Forty-three patients (53%) achieved remission (<15 eosinophils/hpf). Esophageal Candida was reported in 1 patient. Fasting morning cortisol concentrations were low in 10 of 31 patients tested. Six of these 10 patients had abnormal adrenocorticotrophic hormone stimulation testing, 5 of 6 diagnosed with adrenal insufficiency before transition to CIC and 3 of 6 with subsequent normalization of adrenal function on CIC therapy. **CONCLUSIONS:** Patients with EoE treated with CIC experienced significant reductions in clinicopathological features of EoE. CIC can be considered an alternative therapy in patients with known adrenal insufficiency or at risk of developing adrenal insufficiency. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

Key words: Esophageal inflammation; Swallowed topical steroids; Pediatric; Adolescent

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, clinicopathologic disease in which patients demonstrate symptoms related to esophageal dysfunction in the setting of esophageal eosinophilia.¹ Current therapeutic options that target EoE inflammation include dietary elimination therapy, proton pump inhibitors, swallowed topical steroids (STSs), and esophageal dilation. STSs are the most effective pharmacologic option leading to remission in 70% to 80% of patients,²⁻⁴ although presently, no Food and Drug Administration–approved STS formulations exist in the United States. The most commonly used formulations in EoE are swallowed fluticasone propionate (FP) and oral viscous budesonide (OVB), both of which are similarly efficacious.⁵ As with all corticosteroid medications, concerns remain that long-standing use of STS may lead to systemic complications. Reports of adrenal insufficiency (AI) associated with STS use range from 5% to 66%,⁶⁻⁹ suggesting a need for STS options with less risk of suppressing adrenal function.

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Abbreviations used

ACTH- Adrenocorticotrophic hormone

AI- Adrenal insufficiency

CIC- Ciclesonide

des-CIC- Desisobutyl-ciclesonide

EoE- Eosinophilic esophagitis

EREFS- Endoscopic reference score

FP- Fluticasone propionate

OVB- Oral viscous budesonide

STS- Swallowed topical steroid

Ciclesonide (CIC) is a topical corticosteroid used to treat asthma and allergic rhinitis. CIC delivers potent local STS activity with less systemic bioavailability than existing formulations.¹⁰ CIC is delivered as a prodrug that is converted by epithelial esterases to the active form desisobutyl-ciclesonide (des-CIC).^{11,12} des-CIC has 100-fold greater glucocorticoid receptor-binding affinity than CIC and 12-fold greater affinity than dexamethasone.¹³ Our previous work showed that, similar to airway epithelium, the esophageal epithelium expresses carboxylesterases 1 and 2, enzymes required for conversion of CIC to des-CIC.¹⁴ Both CIC and des-CIC form reversible lipid conjugates that act as a drug depot. These localized conjugates increase the duration of action in the treatment of asthma.¹¹

CIC local activity is clinically equivalent to fluticasone,¹³ whereas systemic bioavailability is estimated at less than 1% of fluticasone.^{15,16} In addition, a previous asthma study showed that only 17% of the CIC deposited in the oropharynx was converted to active des-CIC.¹⁷ Thus, lower systemic bioavailability may lead to a less suppressive effect on the hypothalamic-pituitary-adrenal axis, and less active drug in the oropharynx may lead to fewer cases of oral candidiasis compared with patients treated with fluticasone.^{17,18} CIC may therefore be a treatment option to consider in patients with EoE also on corticosteroid preparations for other atopic disease, patients requiring high STS doses for EoE disease control, or those with recurrent oral candidiasis. In this study, we examine whether CIC is an STS that can effectively induce or maintain histologic remission and clinical improvement in patients with EoE. In addition, we sought to determine the impact of CIC with regard to potential adverse effects.

METHODS**Study design**

We performed a retrospective observational cohort study of all children with EoE who were treated with CIC and cared for at Children's Hospital of Colorado from 2010 through 2019. A search of the Epic electronic medical record was conducted (H.M. and M.N.), and all patients between the ages of 2 and 23 years, diagnosed with EoE, who were prescribed CIC treatment were identified for review. Patients who had clinical, endoscopic, and histologic data pre-CIC and post-CIC treatment (after a minimum of 5 weeks of prescribed CIC) were included for study. EoE diagnosis was based on the clinicopathologic findings of esophageal symptoms and esophageal biopsies at diagnosis with more than 15 eosinophils/hpf.¹⁸

A RedCap database was established to compile patient data including demographic characteristics, comorbid atopic diagnoses (asthma, allergic rhinitis, atopic dermatitis), concomitant steroid therapies for other atopic disease, and the reason for transition to

CIC. We recorded clinical findings (growth parameters, symptoms, oral/esophageal candidiasis, morning cortisol levels) as well as endoscopic and histologic findings before and after CIC treatment. Symptoms were recorded on the basis of clinic documentation at time of initiation of CIC and then either resolution or continuation on follow-up. The endoscopic reference score was recorded from endoscopic reports or when not available, determined from images (M.N.) taken at the time of the endoscopy.^{19,20}

Morning cortisol levels were recorded if obtained from 6 months before initiation of CIC until 6 months after the post-CIC endoscopy. Serum cortisol levels were drawn between 7 and 9 AM after at least an 8-hour fast and were considered low if 2 separate levels were less than 5.0 µg/dL. If the fasting morning cortisol level was less than 5.0 µg/dL on 2 occasions, the patient was referred for endocrinologic consultation and 1 µg cosyntropin adrenocorticotrophic hormone (ACTH) stimulation test. For stimulation testing, patients fasted after midnight, with medications held on the morning of the test. Cortisol levels were drawn at baseline and 30 and 60 minutes after the administration of cosyntropin, and AI diagnosis was made by peak cortisol less than 18 µg/dL. ACTH stimulation tests, new fractures, endocrinology follow-up, and stress dose steroids prescribed during this time period were recorded for each subject. The study was approved by the local institutional review board.

Statistical analysis

Categorical variables were summarized with number and percentages in each category. Continuous variables were presented as mean and/or median and range. Comparisons between pre- and post-CIC data were done using paired *t* tests. Statistical significance was defined as *P* less than .05. Microsoft Excel Version 16.47.1 (Microsoft Corporation, Redmond, Wash) and STATA 16.1 (StataCorp LLC, College Station, TX) were used for statistical analysis.

RESULTS**Patient population**

In the time frame examined, 281 CIC-treated patients were identified. Of these, 81 patients (76.5% males and 23.5% females) had pre- and post-CIC endoscopic and histological data available. The average age of the study participants was 9.5 years (2-23 years; Table 1).

Treatments

Of the 81 subjects, 62 (76.5%) had previously been treated with another STS for EoE and the remaining were STS naive (*n* = 19). Forty-one percent (*n* = 33) were treated with an additional topical steroid formulation (inhaled, intranasal, or dermatologic) for a concomitant atopic disease. Of this group, 5 subjects were treated with 2 additional steroid formulations. One patient was treated for 1 week with Medrol 16 mg daily during the change from swallowed FP to CIC.

Reasons for change to CIC included lack of response to other therapies (other STS or elimination diet), behavioral issues (eg, irritability), insurance issues (previous STS no longer covered), risk of adrenal insufficiency (determined by family or provider due to history of AI or receiving multiple steroid preparations), recurrent *Candida* infection (oral or esophageal; diagnosed visually or on biopsy), confirmed adrenal insufficiency, and other issues (concern for side effects, issues with other STS formulations, or not stated). The most common reason for changing to CIC was lack of response to other therapies. Patients were treated with a range of doses of CIC, between 80 µg (2 puffs swallowed

twice daily) to 160 µg (2 puffs swallowed twice daily). Initial dosage was determined by age on the basis of CIC drug insert dosing recommendations for asthma.²¹ Those younger than 12 years were started on CIC at 80 µg (2 puffs twice daily) and those older than 12 years were started at 160 µg (2 puffs twice daily) (Table I).

Symptoms

At the beginning of treatment, 24 patients (29.6%) were asymptomatic, whereas 57 patients (70.4%) reported at least 1 symptom. Of those patients who were symptomatic at the start of the study, 43 (75%) had improvement in at least 1 initially reported symptom and 39 (68%) had complete resolution of all initially reported symptoms. Individual symptom responses are shown in Figure 1.

Mucosal appearance

Endoscopy was performed before initiation of CIC and then repeated after an average of 11.5 months of CIC treatment (range, 2-42 months). A total of 79 patients had pre-CIC and post-CIC endoscopic reports available for evaluation. Two patients had endoscopies done elsewhere, and media was not available for review. Endoscopic reference scores (EREFSs) decreased significantly following CIC treatment (Figure 2). Individual inflammatory EREFS components including edema, exudates, and furrows significantly decreased, whereas more chronic findings of rings and strictures were not significantly changed.

Histological response

CIC treatment significantly decreased mucosal eosinophilia, with peak eosinophil count per hpf reduced from 48 to 23 on pre-CIC compared with post-CIC endoscopy ($P < .001$) (Figure 3). Using less than 15 eosinophils/hpf to define histologic remission, 17.3% were in histologic remission before starting CIC (due to previously attempted treatments). At follow-up endoscopy, 53% met criteria for histologic remission ($P < .001$). The average peak eosinophil count was higher in the distal esophagus compared with the proximal esophagus before and after CIC therapy ($P < .001$); however, both locations showed significant reduction post-CIC ($P < .001$). When assessing histologic response using a more strict criteria of less than 6 eosinophils/hpf, 11 patients (14%) met criteria before CIC initiation compared with 36 patients (44%) after CIC treatment ($P < .001$). Subanalysis of STS-naïve patients ($n = 19$) and nonnaïve patients ($n = 62$) both demonstrated significant improvement with CIC treatment (STS-naïve 5.3% pre- vs 63.2% post-CIC esophageal biopsies <15 eosinophils/hpf, $P < .001$, and STS-nonnaïve 21% pre- vs 50% post-CIC esophageal biopsies <15 eosinophils/hpf, $P = .001$). With regard to age, adolescents and young adults aged 12 to 23 years ($n = 25$) had lower response compared with younger patients aged 2 to 11 years ($n = 56$; 32% vs 62.5% with <15 eosinophils/hpf on post-CIC). Preschool-aged patient's response rate did not differ compared with school-age children. Average length of CIC prescription was 35 weeks before follow-up endoscopy. Histologic response was higher for patients treated longer than 16 weeks as compared with a shorter treatment course (5-16 weeks), with 55% ($n = 56$) versus 44% ($n = 25$) with less than 15 eosinophils/hpf ($P = .02$). There were no differences in peak eosinophil count between these 2 groups before initiation of

TABLE I. Subjects' demographic characteristics

Demographic characteristics (n = 81)	
Age (y), mean (range)	9.5 (2-23)
Sex: male, %	76.5
White, %	87
Hispanic/Latino, %	5
Black/African American, %	3.7
More than 1 race, %	3.7
CIC dose (total daily dose; µg)	
Average	547
Median	640
Range	160-1280
Concomitant atopic disease, %	
Asthma	47
Allergic rhinitis	44.4
Atopic dermatitis	21
None	29.6
Reason for change in corticosteroid, n (%)	
Lack of response to other therapies	45 (56)
Behavioral	11 (13)
Insurance	10 (12)
Risk of AI	9 (11)
Recurrent <i>Candida</i>	6 (7)
Confirmed AI	3 (4)
Other*	8 (10)
Concomitant treatment, n (%)	
Diet	51 (63)
Proton-pump inhibitor	43 (53)
Other corticosteroid for concomitant atopic conditions	33 (41)
Growth data	
Height (Z score)	
Pre-CIC	-0.288
Post-CIC	-0.269
Weight (Z score)	
Pre-CIC	-0.317
Post-CIC	-0.243

Height and weight Z scores were not calculated for 2 patients who were older than 20 y at time of initial endoscopy. A third patient did not have growth parameter data available.

*"Other" reasons for change in corticosteroid included concern for side effects, issues with administration of other STS formulations, or not stated.

CIC. There was no difference in histologic response based on dose of CIC prescribed.

Adverse reactions

Candida infection was diagnosed in 5 patients before initiation of CIC therapy, and in 1 patient post-CIC treatment ($P = .045$). The only patient with identified *Candida* after transition to CIC had 3 previous episodes of *Candida* esophagitis on swallowed FP. Z scores for height, weight, or body mass index were not significantly different pre-CIC and post-CIC treatment.

Cortisol level

A screening, fasting AM cortisol was measured in 31 patients within the time frame of 6 months earlier until 6 months after starting CIC and was abnormal in 10. ACTH stimulation testing result was abnormal in 6 of these 10 patients, and endocrinology consultation did not identify any other noniatrogenic etiologies

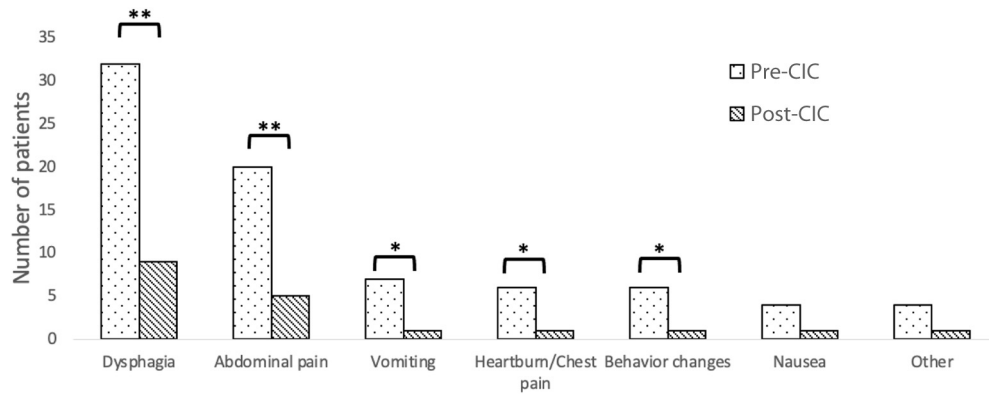


FIGURE 1. Symptom response to CIC. Symptoms reported at the time of initial endoscopy before initiation of CIC and after treatment with CIC. At time of follow-up, symptoms reported as same, improved, or unknown (* $P < 0.05$, ** $P < .001$).

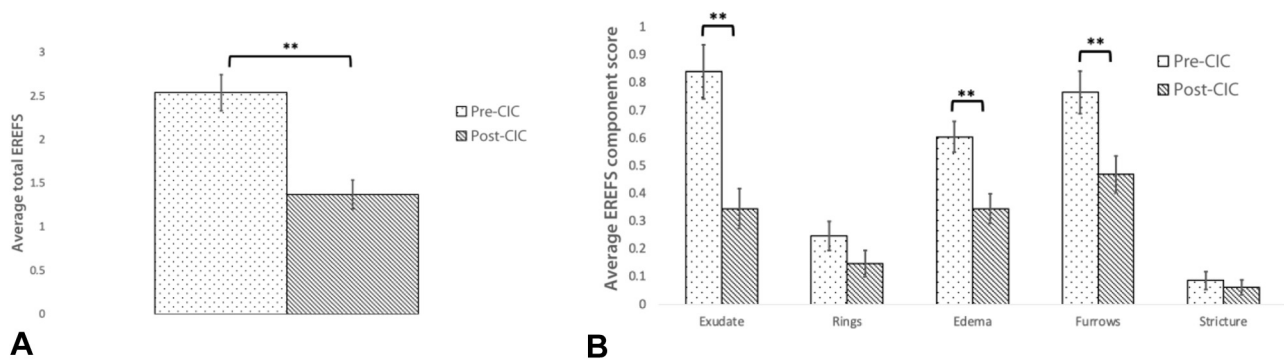


FIGURE 2. Change in EREFS after initiation of CIC. (A) Average total EREFS at endoscopy before initiation of CIC and after treatment with CIC. (B) Average EREFS component scores before initiation of CIC and after treatment with CIC (** $P < .001$).

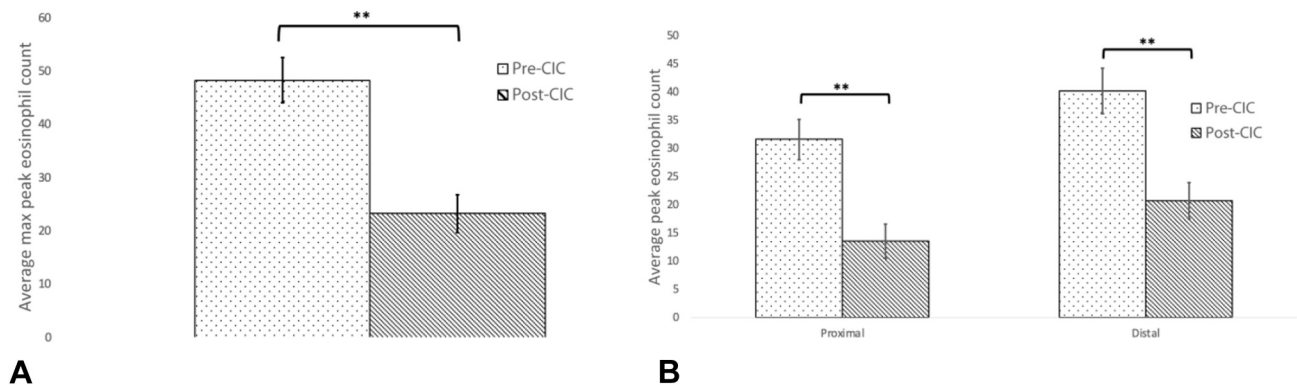


FIGURE 3. Change in peak eosinophil count after initiation of CIC. (A) Average maximum peak eosinophil count from esophageal biopsies at endoscopy before initiation of CIC and after treatment with CIC. (B) Change in maximum peak eosinophil count in proximal and distal esophageal biopsies at endoscopy before initiation of CIC and after treatment with CIC (** $P < .001$).

for AI. Of those with confirmed AI, 4 were on additional steroid therapies for concomitant atopic disease and all were prescribed stress dose steroids.

All 6 patients with AI continued treatment with CIC. Within this AI subgroup, 5 of the 6 patients had been transitioned to CIC because of known AI, 3 of whom experienced normalization of adrenal function while on CIC treatment. The only patient

who developed AI while on CIC had previously been diagnosed with iatrogenic AI in the setting of inhaled steroids used for asthma therapy. This patient had not previously been treated with STSs for EoE and had recurrence of AI 15 months after CIC was started. Three of the 6 patients diagnosed with AI required ongoing stress dose steroid precautions without normalization of adrenal function (based on repeat ACTH

stimulation testing) during the study period. None of the 81 patients exhibited clinical features of AI, and no one diagnosed with AI had adrenal crises or fractures documented during the study period.

DISCUSSION

The most effective medical therapy to date for EoE is the use of STSs, either with OVB or with swallowed FP. CIC is another topical steroid formulation used to treat asthma that was developed to increase local bioavailability at the epithelial surface. We began treating patients with EoE who were nonresponsive to OVB or FP or who were at risk for/had acquired steroid side effects with CIC to provide a potent, less systemically bioavailable therapeutic option. Interestingly, economic factors such as lack of insurance payment for OVB or FP also dictated a change to CIC in some cases. Although the number of CIC-treated patients represents a small fraction of our STS-treated patients with EoE, here we report our 10-year experience with CIC treatment of EoE. Our results demonstrate that CIC reduces symptoms, mucosal abnormalities, and esophageal eosinophilia with few associated side effects, thus supporting its use in the treatment of patients with EoE.

With the increased prevalence of EoE in adults and children, new approaches to treatment with favorable side-effect profiles are urgently needed. Ideal therapeutics successfully treat the clinicopathological features of EoE and minimally impact a patient's quality of life. Novel biologics are under study and provide great promise but are expensive and as of yet unavailable. Even after biologics become available, the need will persist for optimization of easily accessible STS preparations. Currently, although both OVB and FP provide favorable results with limited side-effect profiles, alternative approaches are needed for those who are unresponsive or intolerant to these medications. With the inclination that CIC might have increased local epithelial STS bioavailability,¹¹ we initially determined that esophageal epithelial cells express the necessary esterases to convert CIC to its active form. This was published in a small case series that also found it to be effective in reducing the clinicopathological features of EoE.¹⁴ In a subsequent case series of 4 pediatric patients with EoE, Lee et al²² documented 50% histologic remission without comment on symptomatic change.

In this retrospective study, use of CIC reduced associated symptoms and improved endoscopic and histological features of EoE. Most symptomatic patients had improvement in their symptoms (75%), specifically those with dysphagia and abdominal pain. This is noteworthy considering that other therapeutic studies have shown that mucosal and histologic healing does not always correlate with a reduction of symptoms.²³ In terms of mucosal healing, there were significant improvements in edema, exudates, and furrows, which are thought to reflect the inflammatory signs of EoE.^{24,25} However, EREFS components of rings and strictures were not significantly decreased, likely due to inadequate power, because few rings and strictures were noted in this cohort.

With regard to histologic efficacy, 53% of patients improved to, or maintained, esophageal eosinophilia less than 15 eosinophils/hpf while on CIC. Notably, 29% of patients with persistent inflammation despite initial treatment with a first-line STS formulation improved to less than 15 eosinophils/hpf on CIC. This significant improvement in patients who had previously

been steroid nonresponsive may reflect the localized CIC conversion to the more potent active compound des-CIC and from increased mucosal exposure due to lipid conjugation.

The effectiveness found in this study population is lower than what has been reported for other STS formulations. This is likely influenced by steroid nonresponsiveness, duration of treatment, age, and possibly adherence. Most of our study population (56%) transitioned to CIC because of lack of response to other therapies, suggesting a more treatment-resistant population. An increased rate of effectiveness was shown in those who were STS-naïve at the time of initiation of CIC, with 60% improvement to less than 15 eosinophils/hpf. In addition, those subjects who received longer duration of CIC treatment (>16 weeks) before repeat endoscopy had increased rate of improved histology. When limiting analysis to steroid-naïve subjects treated for more than 16 weeks before follow-up endoscopy, 67% improved to less than 15 eosinophils/hpf. Subanalysis dividing the cohort into different age groups showed that efficacy in the older 12- to 23-year-old age group was much lower than in the younger age groups. This may be due to medication nonadherence in this age group or other unknown confounders.²⁶ This difference in age response is of interest because a dose-response was not identified. Lack of a dose-response may have been due to older, larger patients receiving higher dosages compared with younger, smaller patients, thus maintaining a consistent dose per body surface area. Alternatively, this could be a result of lower adherence and therefore lower effectiveness in the older, higher dose, age group. Lastly, very young patients (eg, age 2-5 years) may have difficulty in directing the medication effectively to the esophagus.

Although our initial dosing of CIC was based on its use in treating asthma, lower doses may still be therapeutic for EoE. A 2006 randomized, placebo-controlled study evaluated 1018 patients with asthma aged 4 to 11 years who were treated with once-daily CIC. For age-based dosages of 40, 80, and 160 µg, the results showed that once-daily dosing led to equivalent improvement in FEV₁ when compared with twice-daily dosing.²⁷ Based on its pharmacology, this impact is likely a result of the previously described mechanism of the longer mucosal contact time of CIC due to drug-lipid conjugates.¹¹ Whether this is true for the squamous epithelium of the esophagus remains uncertain. Future prospective study is needed to determine appropriate dosing as well as to monitor adherence.

In the limited number of patients evaluated for AI, we did not find that CIC led to development of adrenal dysfunction. Only 1 patient with a previous history of iatrogenic AI secondary to asthma medications developed AI while being treated with CIC. This rate is lower than the rates of adrenal suppression reported with other STS formulations.⁷ Despite the fact that OVB and FP have limited absorption, frequencies of reported AI have been widely disparate, ranging from 5% to 66%.⁶⁻⁹ We anticipate that the low rate of AI in this study is related to the localized mechanism of epithelial esterase cleavage to active des-CIC and the high protein binding, which limits systemic bioavailability. The potential development of AI in patients with EoE poses an important consideration in the care of those treated with STSs. Patients with EoE with AI can easily be missed because it is uncommon and most patients with AI, including all of those in our series, are asymptomatic. This is of concern because patients with EoE encounter numerous stressful events, including frequent endoscopic procedures that require anesthesia. Our previous study found that most patients with EoE treated with

STSs who developed AI were treated with more than 1 topical steroid.⁸ Thus, limiting the dose, potency, and number of topical steroid treatments for patients with EoE remains an important goal and when possible, the use of a preparation with less systemic bioavailability such as CIC would be beneficial.

The retrospective nature of our study limits conclusions because adherence, impact of comorbid allergic diseases and treatments, and comparisons to other STS preparations cannot be assessed. Not all CIC patients were evaluated for AI, but of those who were and were found to have low cortisol levels, all underwent a thorough evaluation by an endocrinologist.

We examined 81 patients with EoE treated with CIC and found that 75% had improvement in initially reported symptoms and 53% of subjects developed or maintained histologic response; those patients previously STS-naïve and/or with longer duration of treatment had a higher rate of histologic response. The side-effect profile was minimal, with no increased rate of adverse drug reactions or adrenal suppression. Thus, this retrospective study supports that CIC can be considered as an STS for the treatment of EoE. CIC may be particularly useful to consider in patients at risk for, or with side effects of, other STS formulations. Future prospective studies will be needed to determine efficacy in comparison to other STSs, the most efficacious dose and dosing interval, and whether CIC is truly less adrenally suppressive than other topical steroid preparations.

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