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Effect of Intranasal Corticosteroids on Allergic Airway Disease in Asthma

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Asthma; rhinitis; sinusitis; sinonasal; asthma control; lung function

Dear Editor

Chronic sinonasal disease is common in asthma, and associated with poor asthma control. We recently completed a study of intranasal corticosteroids in patients with chronic sinonasal disease and poorly controlled asthma, and found no significant effect of nasal corticosteroids on asthma control over 24 weeks.[1] Although we did not find an effect on asthma control overall, we hypothesized that intranasal corticosteroids might decrease airway markers of allergic inflammation with chronic treatment, and also improve asthma control specifically during allergy season.

We analyzed data from this randomized, double-masked, placebo-controlled trial of nasal mometasone versus placebo in adults and children with poorly controlled asthma.[1] Eligibility criteria included physician diagnosed asthma, age ≥ 6 years, poorly controlled asthma[2] and chronic sinonasal disease (diagnosed by questionnaire[3]). Participants were excluded who had used systemic or nasal corticosteroids within the prior 4 weeks, and anti-leukotriene medication within the prior 2 weeks. Participants were allowed to use anti-histamines for symptom control. Participants ≥ 12 years received 100 mcg of mometasone or placebo, those ages 6 to 11 years received 50 mcg mometasone or placebo per nostril daily.

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Study drug and placebo provided by Merck (Merck had no role in designing, conducting, or approving the study or analyzing the results).

We first compared the effects of 24 weeks of intranasal corticosteroids on markers of allergic airway inflammation. Fractional oral exhaled nitric oxide (FeNO) was measured at baseline and week 24 (Insight eNO System, Apieron, CA). Nasal lavage was performed at baseline and 24 weeks.[4] Samples were shipped to one center, and eosinophilic cationic protein and CCL17 measured by ELISA assay, according to manufacturer's recommendations NovaTeinBio (Boston, MA) and R&D Systems (Minneapolis, MN).

Then we conducted an analysis of the effect of intranasal corticosteroids on asthma control in weed allergic participants during weed allergy season. We limited our analysis to weed pollen season, based on prior reports suggesting weed allergens are significantly related to poorly controlled asthma. Allergy testing was performed as previously described.[1] We included only participants at centers_with available pollen counts (provided by the provided by the National Allergy Bureau™), and a clearly defined weed allergy season (ALA-ACRC centers east of the Rockies, and excluding centers in the South). We defined "in season" as beginning on the first of 3 days with pollen counts ≥ 10 grains/mm^3, and ending on the last day of the last occurrence of 3 consecutive days with pollen counts of ≥ 10 grains/mm^3. Diary cards were used to assess asthma and sinus symptoms, rescue medication use, and health care use during allergy season.

The sample size was based on that for the mainline study.[1] Kruskal-Wallis and Chi-squared tests were used to evaluate subgroup differences for continuous and categorical variables, respectively. T-tests and linear regression were used to evaluate treatment differences in the change from baseline to 24 weeks. An interaction term was added to the model to evaluate whether the treatment effect differed by age (pediatric vs adult). Negative binomial regression was used to assess the effect of treatment on event rates for weed allergic participants over the entire course of the study. A mixed model with a person-level random effect was used to evaluate seasonal differences in the rates to account for repeated measurements (in season and out of season). Kruskall-Wallis tests were used to compare the proportion of days with symptoms, medication, and events for the two treatment groups as well as for the combinations of treatment and season. Analyses were performed with SAS 9.4 (Cary, NC).

Demographics are shown in Table E1, adults had significantly more sinus symptoms than children, however, there was no effect of nasal mometasone on nasal, airway or serum markers of allergic airway inflammation (Table 2). Demographics of weed allergic participants studies are shown in Tables E2 and E3. There was no seasonal variation in the effect of mometasone on episodes of poorly controlled asthma (Table 2). We found a slight numeric increase in episodes of poorly controlled asthma, and decrease in asthma and rhinitis symptom free days in season compared with out of season, but this did not reach statistical significance (Table E4).

These data show that 24 weeks of nasal mometasone does not affect markers of allergic airway inflammation in study participants with chronic sinonasal disease and poorly controlled asthma. Nor is there a reduction in the risk of having episodes of poorly controlled asthma in weed-allergic participants treated chronically with mometasone overall, or within the allergy season.

Prior short-term studies show that nasal corticosteroids reduce nasal ECP[5] and exhaled nitric oxide[6] in asthma during allergy season, but we are not aware of any longer term studies showing that chronic nasal corticosteroids reduce these markers of eosinophilic inflammation in asthma.

Many, but not all publications, have described an effect of intranasal corticosteroids on asthma during allergy season.[7] We did not see a significant effect of nasal steroids on seasonal nasal symptoms, but our study differed from others in that we treated asthmatic participants chronically with nasal corticosteroids, rather than just during allergy season, and perhaps this may have affected the response to treatment.

Many studies of long term treatment of allergic rhinitis show that nasal corticosteroids improve inflammation[8] and prevent seasonal worsening of symptoms,[9] but these were not studies in patients specifically with asthma. It is possible that asthmatics have more steroid-resistant sinonasal disease, or orally inhaled corticosteroids have some effect in the upper airway, such that the addition of nasal corticosteroids does not produce a marked additive effect on sinonasal disease.

The sample size for studying the efficacy of chronic nasal corticosteroids in allergy season was smaller than for the main study, but given the wide confidence intervals for the outcomes, any effect of nasal corticosteroids on asthma is likely to be small.

Our study suggests that chronic treatment of sinonasal disease with nasal corticosteroids is likely to have minimal effect on asthma, and that chronic treatment of asthmatics with nasal corticosteroids does not affect seasonal asthma or nasal symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Implications

Sinonasal disease is associated with poor asthma control, but nasal steroids alone may not be sufficient to significantly impact sinonasal disease in patients with asthma.

Table 1

Effect of nasal mometasone on markers of allergic airway inflammation at 24 weeks

Characteristic	N	Mometasone Median (Q1, Q3)	N	Placebo Median (Q1, Q3)	P-value*	Interaction P-value*
Nasal Thymus and activation-regulated						
BL	71	21.9 (14.4, 37.7)	75	20.0 (13.6, 35.7)		
24 week	57	21.2 (13.0, 32.4)	62	20.4 (11.8, 33.3)		
Δ 24 week	57	−3.3 (−16.1, 7.3)	61	−0.2 (−6.3, 5.3)		
Adult					0.52	0.95
BL	112	19.2 (11.4, 29.2)	114	21.6 (13.3, 35.8)		
24 week	92	17.8 (10.0, 27.1)	93	19.6 (11.25, 32.6)	0.17	
Δ 24 week	91	−1.5 (−7.4, 3.2)	90	−1.0 (−9.3, 4.6)		
Nasal lavage Eosinophil Cationic Protein						
Pediatric						
BL	71	26.8 (10.6, 51.9)	75	31.0 (18.1, 52.4)		
24 week	57	31.6 (13.2, 49.4)	60	38.7 (13.5, 55.0)		
Δ 24 week	57	5.1 (−8.4, 21.6)	59	0.2 (−20.4, 16.5)	0.97	
Adult						0.85
BL	110	12.5 (3.3, 39.4)	110	9.5 (2.2, 37.5)		
24 week	91	9.6 (2.3, 38.0)	95	12.7 (1.8, 53.8)		
Δ 24 week	89	0.8 (−5.1, 15.2)	90	−0.1 (−10.6, 10.2)	0.79	
Serum CCL17						
Pediatric						
BL	67	343.9 (249.4,519.0)	75	366.4 (240,501.1)		
24 week	56	312.6 (238.4, 458.6)	62	377.0 (240.1,484.8)		
Δ 24 week	55	−10.7 (−77.1, 18.4)	60	−18.4 (−80.3, 32.9)	0.79	
						0.98
Adult						
BL	107	294.8 (210.0, 409.4)	110	359.2 (242.1, 476.8)		
24 week	87	302.6 (189.0, 460.4)	92	344.0 (209.4, 462.0)		
Δ 24 week	83	−11.3 (−66.3, 28.9)	86	−26.2 (−65.0, 37.8)	0.74	

Characteristic	N	Mometasone Median (Q1, Q3)	N	Placebo Median (Q1, Q3)	P-value*	Interaction P-value*
Serum Eosinophil Cationic Protein						
Pediatric						
BL	68	4.8 (2.2, 13.3)	75	5.5 (1.6, 14.7)		
24 week	56	6.2 (2.4, 10.9)	63	4.7 (2.3, 16.0)		
Δ 24 week	56	0.1 (−1.7, 1.4)	61	−0.05 (−3.2., 2.0)	0.64	
Adult						0.94
BL	110	8.5 (4.3, 21.5)	115	9.5 (4.6, 20.1)		
24 week	89	8.4 (2.8, 18.5)	97	7.8 (4.2, 17.4)		
Δ 24 week	87	−0.8 (−5.6, 2.0)	94	−0.1 (−5.9, 2.3)	0.63	
Oral Fractional Exhaled Nitric Oxide (FeNO)						
Pediatric						
BL	71	30.5 (16.5, 47.5)	76	29.5 (16.5, 44.0)		
24 week	58	32.5 (14.0, 58.5)	65	31.0 (18.5, 52.5)		
Δ 24 week	57	0.5 (−6.5, 19.0)	62	3.0 (−3.0, 17.0)	0.39	0.54
Adult						
BL	113	23.0 (15.0, 41.5)	116	25.0 (16.3, 47.5)		
24 week	90	21.5 (13.5, 37.5)	93	26.0 (18.5, 53.0)		
Δ 24 week	88	−1.0 (−6.3, 6.5)	91	0.5 (−7.0, 10.0)	0.75	

*P-values were calculated using linear regression with the differences as the dependent variable

BL = baseline, Δ 24 week = change from BL to 24 weeks.

Table 2

Rates of Episodes of Poorly Controlled Asthma, and Daily Asthma and Rhinitis Symptoms in and out of weed season for participants allergic to weeds

	Out of season				*In Season*				
Asthma Event Type									
Rates*	***Placebo Events/ Person year*** *Mean (95% CI)**	***Mometasone Events/Person year*** *Mean (95% CI)**	***Relative Risk Mometasone/ Placebo*** *(95% CI)**	***P-value****	***Placebo Events/ Person year*** *Mean (95% CI)**	***Mometasone Events/Person year*** *Mean (95% CI)**	***Relative Risk Mometasone/ Placebo*** *(95% CI)**	***P-value****	***Interaction P-value**†***
N	*45*	*32*	*75*		*39*	*22*	*60*		
EPACS overall	*2.11 (1.44, 3.10)*	*2.53 (1.43, 4.48)*	*1.44 (0.67, 3.11)*	*0.35*	*2.36 (1.08, 5.16)*	*1.79 (0.47, 6.79)*	*0.58 (0.12, 2.79)*	*0.49*	*0.12*
↓ Peak Flow exacerbation	*0.95 (0.51,1.79)*	*0.99 (0.38, 2.54)*	*1.08 (0.30, 3.82)*	*0.91*	*1.02 (0.22, 4.66)*	*0.47 (0.03, 6.79)*	*0.22 (0.01, 4.53)*	*0.32*	*0.07*
↑ Rescue Medications	*1.29 (0.77, 2.17)*	*1.52 (0.70, 3.33)*	*1.39 (0.49, 3.92)*	*0.54*	*1.43 (0.48, 4.24)*	*1.61 (0.27, 9.84)*	*1.28 (0.15, 11.25)*	*0.83*	*0.80*
Oral Steroids	*0.45 (0.19,1.07)*	*0.52 (0.14,1.92)*	*1.34 (0.24, 7.61)*	*0.74*	*‡*	*‡*	*n/a*	*n/a*	
	Placebo *Median (Q1, Q3)*	***Mometasone*** *Median (Q1, Q3)*		***P-value****	***Placebo*** *Median (Q1, Q3)*	***Mometasone*** *Median (Q1, Q3)*		***P-value****	***Interaction P-value****
Asthma Symptoms									
% symptom free days	*48.25 (8.41, 73.15)*	*35.44 (1.78,82.09)*		*0.55*	*32.26 (0, 89.80)*	*16.98 (0.00, 90.32)*		*0.81*	*0.78*
% nights woken by asthma	*3.45 (0, 11.45)*	*1.82 (0,7.81)*		*0.92*	*0.00 (0.00, 8.33)*	*0.00 (0.00, 30.00)*		*0.56*	*0.58*
Rhinitis Symptoms									
% Rhinitis Symptom Free days	*28.91 (1.82, 57.32)*	*7.94 (0, 52.77)*		*0.18*	*26.67 (0, 87.80)*	*0.00 (0.00, 32.92)*		*0.07*	*0.09*
% Rhinitis Rescue Medication use days	*0.00 (0.00,2.82)*	*0.00 (0.00, 3.04)*		*0.71*	*0.00 (0.00, 0.00)*	*0.00 (0.00, 0.00)*		*0.83*	*0.25*

An episode of poor asthma control was defined as any one of the following: a decrease of greater than 30% in morning peak flow rate from personal best (assessed during run-in) for 2 consecutive days, addition of an oral corticosteroid to treat asthma symptoms, unscheduled contact with a health care provider for asthma symptoms or increased use of short acting β-agonists (≥ 4 additional puffs of rescue medication or ≥2 additional nebulizer treatments in 1 day).

Rhinitis symptoms were defined as runny nose, nasal congestion, itching or sneezing

*Rate ratios and p-values are calculated from a negative binominal model

†P-values for the test of interaction between treatment and weed season are based upon a negative binomial model with a random effect for individual.

‡There were no oral steroid exacerbations for individuals who were in season

** -values based upon Kruskall Wallis test

EPACS = Episodes of poor asthma control; Q1 = 1st quartile; Q3 = 3rd quartile; % = percent.

Definitions:

- EPACS overall: any of the below exacerbations
- ↓ Peak Flow exacerbation: A decrease in peak flow. During a two week run in period for the trial, average peak flow was calculated. If peak flow falls below 70% of this average for two consecutive days, this is considered a peak flow exacerbation
- ↑ Rescue Medications: In the run-in period, average rescue medication use was calculated in units using a nebulizer counts as two puffs of MDI. An exacerbation is if the subject is 4 units increase from the baseline average.
- Oral Steroids: If the subject uses oral steroids to control their breathing, this counts as an exacerbation. There is a 14 day washout period before using oral steroids again will count as a new exacerbation, designed to not count usage from the same episode.

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