

DURATION OF ANTIINFLAMMATORY AND SYMPTOMATIC EFFECTS AFTER SUSPENSION OF INTRANASAL CORTICOSTEROID IN PERSISTENT ALLERGIC RHINITIS

Giorgio Ciprandi, M.D. ⁽¹⁾, Vittorio Ricca, M.D. ⁽¹⁾, Ferrero Paola, B.S. ⁽¹⁾, Bairo Alessandra, B.S. ⁽¹⁾, Anna Maria Riccio, Ph.D. ⁽²⁾, Manlio Milanese, M.D. ⁽²⁾, F.Frati, M.D. ⁽³⁾, Maria Angela Tosca, M.D. ⁽⁴⁾

Summary

■ **Background:** Allergic rhinitis is characterized by an inflammatory response consequent to allergen exposure. Intranasal corticosteroids represent a first line treatment, but there is no adequate knowledge concerning the duration of symptomatic and antiinflammatory effects after their suspension. Thus, we aimed at investigating this issue.

■ **Methods:** Twelve children with persistent allergic rhinitis were treated with FPANS for 30 days and were followed for 12 days after its suspension. Nasal symptoms, considered as TSS, and inflammatory cells, recovered by nasal scraping, were evaluated.

■ **Results:** FPANS significantly reduced TSS ($p<0.0001$), neutrophils ($p<0.001$), and eosinophils ($p<0.0001$) after 4 days of treatment. Symptoms and cellular infiltrate quickly reappeared after suspension (respectively after 3 days for symptoms ($p<0.05$), after 4 days for neutrophils ($p<0.05$), and 6 days for eosinophils ($p<0.001$)).

■ **Conclusion:** These findings suggest that nasal corticosteroid treatment is highly effective in nasal symptoms' relief and inflammation's control, but its suspension induces a rapid reappearance of them.

Key-words: Allergic rhinitis - Inflammatory cells - Nasal symptoms - Suspension - Topical corticosteroids.

INTRODUCTION

Allergic rhinitis is a common disorder characterized by the following nasal symptoms: sneezing, itching, rhinorrhea, and nasal congestion. Symptoms arise as a result of inflammation induced by an IgE-mediated immune response to specific allergens. The immune reaction involves the release of inflammatory mediators and cytokines and the recruitment and the activation of cells to the nasal mucosa. Actually, the eosinophils infiltrating the nasal mucosa may be actually regarded as hallmark of allergic inflammation.

Moreover, if allergen exposure continues, a "minimal persistent inflammation" is always detectable also in symptom-free rhinitics with mite or pollen allergy (1, 2). Therefore, the constant exposure to the allergen, even though it does not induce symptoms, is anyway able to promote, sustain, and maintain inflammation,

detectable for instance by monitoring inflammatory cell infiltration at mucosal level (1, 2).

On the basis of this pathophysiological evidence, ARIA document provided by WHO classify allergic rhinitis as persistent or intermittent in accordance with the duration of symptoms.

Intranasal corticosteroids are considered as first level treatment in patients with persistent allergic rhinitis (3).

Fluticasone propionate is a topically-active corticosteroid molecule based on the androstane nucleus (4). Several studies have demonstrated the efficacy of its formulation as aqueous nasal spray (FPANS) in the treatment of allergic rhinitis, reducing both clinical and inflammatory parameters (4).

Moreover, FPANS inhibites both early- and late-phase responses following allergen-specific nasal challenge, including symptoms, eosinophil infiltrate, and adhesion molecule expression (5).

However, there remains a lack of adequate knowledge concerning the duration of antiinflammatory and

(1) Allergy, Dpt Head-Neck, San Martino Hospital, Genoa Dpt Internal Medicine, Genoa University.

(2) Clinica Tisiologica, Università di Genova.

(3) Clinica Pediatrica universita' di Perugia (Italy).

(4) Istituto Giannina Gaslini, Genova, Koelliker Hospital, Allergy Section (Turin).

symptomatic effects after the suspension of corticosteroid treatment.

Therefore, we designed a study aimed at monitoring the reappearance time-course of symptoms and inflammation in children with persistent allergic rhinitis after the suspension of intranasal corticosteroid treatment.

MATERIALS AND METHODS

The study was designed to evaluate patients with persistent allergic rhinitis during and after an intranasal corticosteroid treatment.

Twelve children were enrolled (5 males and 7 females, mean age 13, ranging 10-17 years) in autumn (period with high levels of mite allergen exposure). All of them were sensitised to house dust mites (*Dermatophagoides pteronyssinus* and *farinae*) only, as confirmed by history, skin prick test, and specific seric IgE.

All children were treated with FPANS 100 mcg once daily (1 spray/each nostril in the morning) for 30 days. Then, the treatment was suspended and the patients were daily monitored for 12 days.

A placebo-group was not considered, since the main scope of this study was the evaluation of the phenomena appearing after the suspension and it was not considered ethical by our Ethics Committee.

Only subjects who met all the following criteria were eligible for inclusion into the study: history of rhinitis due to natural mite allergen exposure for the previous 2 years, rhinitis symptoms at least from 2 previous weeks, and TSS minimum value > 6 at baseline.

Children with a recent upper airway infection, with anatomic nasal problems, or with other significant medical problems were not enrolled as well as patients receiving specific immunotherapy. No other drug was permitted 1 month before and during the study.

The protocol was approved by the Ethics Committee and an informed consent was required before the enrolment.

Evaluated parameters were: i) nasal symptoms (evaluated as TSS of nasal itching and obstruction, sneezing and rhinorrhea, all of them scored with an arbitrary scale at 4 points: 0= absent, 1= mild, 2= moderate, 3= severe) recorded during the visits, and ii) inflammatory cells (i.e. neutrophil and eosinophil number).

A clinical examination was performed in all patients during the corticosteroid treatment every 4 days for 30 days, then patients were observed daily after the suspension for 12 days. A nasal scraping was performed at each visit.

■ **Cytological assessment:** nasal scrapings were obtained according to previous reports (1,2). Briefly, the cotton tip was immersed, after the scraping, into a plastic tray with PBS and transferred to a 10-mL polypropylene tube. Then the recovered fluids were centrifuged at 1400xg for ten minutes and each pellet resuspended in PBS solution (2 mL); cell suspensions were filtered to reduce the quantity of mucus and cytospin slides were prepared using standard techniques.

The differentiation among eosinophils, neutrophils, and epithelial cells were made by May-Grünwald/Giemsa staining. The number of inflammatory cells (neutrophils and eosinophils) was considered as a total number of any cell type/each microscope field: the data were expressed as a mean of 10 fields.

■ **Statistical analysis** was performed using the ANOVA one-way and Duncan post-hoc test, the Wilcoxon matched pairs test, and the Spearman test.

RESULTS

All enrolled subjects completed the study.

■ Treatment period

➤ **Symptoms:** all subjects were symptomatic with a TSS > 6 at the enrolment visit (Figure 1). A significant reduction of TSS was detectable from the first visit, i.e. after 4 days of FPANS treatment ($p < 0.0001$). The TSS values progressively diminished until the last visit, when they were absent in most patients.

Inflammatory cells: an inflammatory infiltrate was present in all patients at baseline (Figure 2). Neutrophils were more abundant than eosinophils. A significant reduction of both neutrophils and eosinophils was evident after 4 days of treatment (respectively $p < 0.001$ and < 0.0001). Neutrophil and eosinophil numbers progressively decreased. Eosinophils were actually absent after 16 days of treatment, showing a strong susceptibility to corticosteroid effect.

There were significant correlations between neutrophils and symptoms ($R = 0.93$; $p < 0.05$) and eosinophils and symptoms ($R = 0.99$; $p < 0.05$)

■ Suspension period

➤ **Symptoms:** they quickly reappeared after 3 days of corticosteroid suspension ($p<0.05$).

Symptoms progressively increased, returning near baseline values after 12 days of suspension; there was no significant difference between day 4 during treatment and day 12 after suspension ($p=n.s.$).

➤ **Inflammatory cells:** neutrophils rapidly increased after suspension, whereas eosinophils more slowly infiltrated nasal mucosa, showing a remarkable influence of corticosteroid antiinflammatory activity.

Neutrophils were significantly increased 4 days after suspension ($p<0.05$); moreover, there was no significant difference between baseline values and 6 days after suspension ($p=n.s.$).

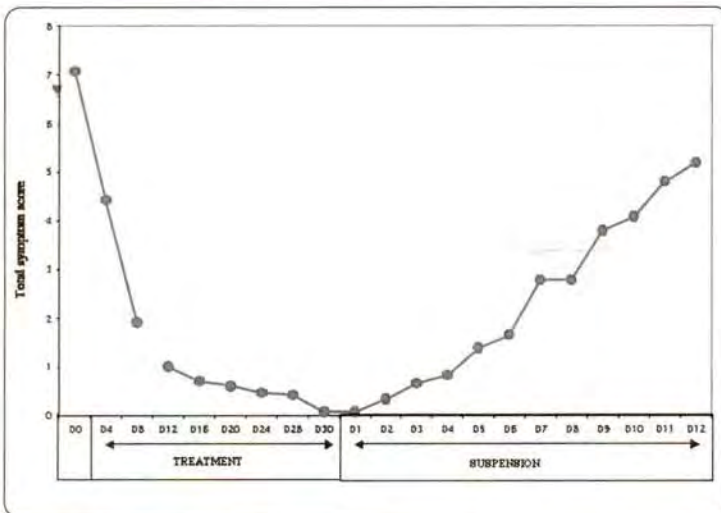


Fig 1 : Nasal Symptoms Total Symptom Scores are reported for all visits: during the treatment and after the suspension.

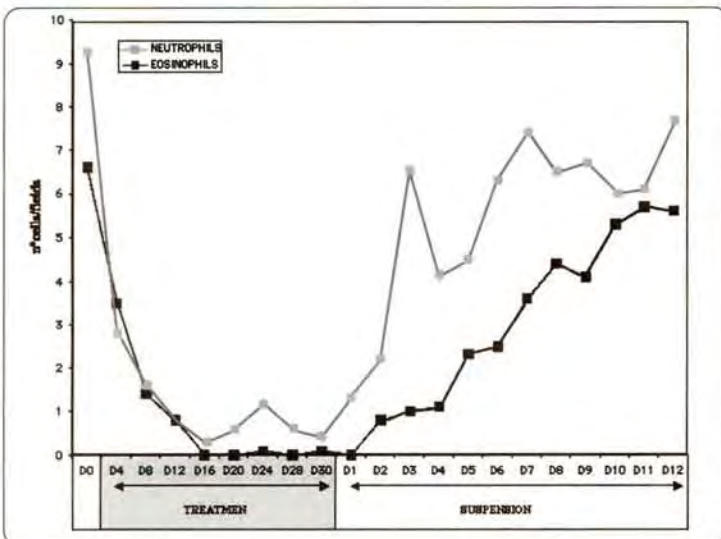


Fig 2 : Inflammatory cells Eosinophil (green squares) and neutrophil (yellow squares) counts in nasal scraping are reported for all visits: during the treatment and after the suspension.

Eosinophils significantly increased 6 days after suspension ($p<0.001$), without difference in comparison with baseline values ($p=n.s.$).

There were significant correlations between neutrophils and symptoms ($R=0.72$; $p<0.05$) and eosinophils and symptoms ($R=0.97$; $p<0.05$).

DISCUSSION

Persistent allergic rhinitis is a new operative classification proposed by ARIA document, which is based on clinical and pathophysiological evidence (6). Persistent allergic rhinitis is considered when symptoms persist for more than 4 days per week and for more than 4 weeks.

The evidence based ARIA document suggests that the global therapeutic strategy for allergic rhinitis should be revised and targetted also to inflammatory phenomena, rather than to symptoms only.

The concept of minimal persistent inflammation represents a crucial aspect of the allergic reaction: the inflammatory response persists until allergen exposure lasts also without symptoms (1, 2).

Thus, an optimal control of allergic inflammation could be achieved by using long-term treatments instead of on demand treatment as recently provided by some clinical experiences (7, 8).

On the other hand, a practical concern for physicians is the duration of the treatment, also considering the dose, the safety and the reappearance of symptoms and inflammation after the suspension.

Thus, this study aimed at investigating the last question.

This study evaluated symptoms and inflammatory parameters, monitoring them during and after a long-term continuous intranasal corticosteroid treatment.

In agreement with literature evidence, both concerning allergen challenge model and natural allergen exposure (3), is our finding that symptoms and inflammatory cells decrease quickly (since the first visit: i.e. after 4 days) and dramatically at the end of corticosteroid treatment. At this regard, onset of therapeutic effect has been reported to occur within 12 hours, and as early as 2 to 4 hours in some patients after administration of the first dose of FPANS (9).

After the suspension of corticosteroid treatment, both symptoms and inflammatory infiltrate quickly reappeared.

The susceptibility of the different inflammatory cells to corticosteroid treatment and the duration of the response after the suspension differ, according to previous studies (10, 11, 12). Eosinophils are very sensitive to corticosteroid treatment: in fact, their significant reappearance occurs after neutrophils.

These findings suggest that the duration of the effects of the corticosteroid is quite short after the suspension, since the allergic inflammation and the symptoms reemerge as consequence of the continuous allergen exposure.

A clinical issue deriving from this evidence is the importance of daily use of topical corticosteroids. In fact, if the drug is not adequately prescribed, symptoms and overall inflammation may not be adequately controlled. As reported in a previous study, the administration of topical corticosteroid on a symptomatic basis showed significantly more symptoms than in patients continuously treated (13). The same finding has been reported using oral antihistamines (7, 8).

This evidence may represent an important knowledge from a clinical point of view.

CONCLUSION

The results of this study indicate that the global therapeutic strategy for allergic rhinitis should be revised and targeted also to inflammatory phenomena, rather than to symptoms only. This could be achieved by using long-term treatments instead of on demand treatment as recently provided by some clinical experiences (7, 8).

Further studies are required to better define the duration of corticosteroid course and suspension, also considering the safety and the possible coadministration of inhaled corticosteroids (since the high preva-

lence of asthma comorbidity, mainly in pediatric patients) to optimize the management of persistent allergic rhinitis.

REFERENCES

1. Ciprandi G., Buscaglia S., Pesce G.-P., Pronzato C., Ricca V., Parmiani S., Bagnasco M., Canonica G.-W. - Minimal persistent inflammation is present at mucosal level in asymptomatic rhinitic patients with allergy due to mites. *J Allergy Clin Immunol* 1995;95:612-21.
2. Ricca V., Landi M., Ferrero P., Bairo A., Tazzer C., Canonica G.-W., Ciprandi G. - Minimal persistent inflammation is present also in patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;105:54-7.
3. van Cauwenberge P., Bachert C., Passalacqua G., Bousquet J., Canonica G.-W., Durham S.-R., Fokkens W.-J., Howarth P.-H., Lund V., Malling H.-J., Mygind N., Passali D., Scadding G.-K., Wang D.-Y. - Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. *Allergy* 2000;55:116-34.
4. Holliday S.-M., Faulds D., Sorkin E.-M. - Inhaled fluticasone propionate. *Drugs* 1994;47 (2): 318-331.
5. Ciprandi G., Ricca V., Passalacqua G., Fasolo A., Canonica G.-W. - Intranasal fluticasone propionate reduces ICAM-1 on nasal epithelial cells both during early and late phase after allergen challenge. *Clin Exp Allergy* 1998;28:293-9.
6. Lockett R.-F. "ARIA": global guidelines and new forms of allergen immunotherapy. *J Allergy Clin Immunol* 2001;108:497-9.
7. Ciprandi G., Passalacqua G., Mincarini M., Ricca V., Canonica G.-W. - Cetirizine continuous versus on demand treatment in allergic rhinitis. *Ann Allergy Asthma Immunol* 1997;79:507-511.
8. Ciprandi G., Ricca V., Passalacqua G., Truffelli T., Bertolini C., Fiorino N., Riccio A.-M., Bagnasco M., Canonica G.-W. - Seasonal rhinitis and azelastine: long or short term treatment? *J Allergy Clin Immunol* 1997;99:301-7.
9. Meltzer E.-O., Rickard K.-A., Westlund R.-E., Cook C.-K. - Onset of therapeutic effect of fluticasone propionate aqueous nasal spray. *Ann Allergy Asthma Immunol* 2001;86:286-291.
10. Holm A.-F., Fokkens W.-J. - Topical corticosteroids in allergic rhinitis, effects on nasal inflammatory cells and nasal mucosa. *Clin Exp Allergy* 2001;31:529-535.
11. Holm A.-F., Godthelp T., Fokkens W.-J. et al. - Long-term effects of corticosteroids nasal spray on nasal inflammatory cells in patients with perennial allergic rhinitis. *Clin Exp Allergy* 1999;29: 1356-1366.
12. Holm A.-F., Dijkstra M., Kleinjan A. et al. - Fluticasone propionate aqueous nasal spray reduces inflammatory cells in unchallenged allergic nasal mucosa: effects of single allergen challenge. *J Allergy Clin Immunol* 2001;107:627-633.
13. Juniper E.-F., Guyatt G.-H., Archer B., Ferrie P.-J. - Aqueous beclomethasone dipropionate in the treatment of ragweed pollen-induced rhinitis: further exploration of "as needed" use. *J Allergy Clin Immunol* 1993;92:66-72.

