

INTRANASAL FLUNISOLIDE TREATMENT IN PATIENTS WITH NON-ALLERGIC RHINITIS

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Non-allergic rhinitis (NAR) is a heterogeneous disease, characterized by nasal hyperreactivity and inflammation. Its treatment is still debated, intranasal corticosteroids may be an option. The present study is aimed at evaluating the effect of the use of intranasal flunisolide in patients with NAR, considering both clinical and cytological parameters. Sixty patients were treated with intranasal flunisolide (30) or saline solution (30) for 8 weeks. Symptom severity, turbinate size, and inflammatory cell counts were assessed, before and after treatment. Intranasal flunisolide induced a significant reduction of symptoms, turbinate size, and cellular infiltrate. Thus, intranasal flunisolide might be a therapeutic option for NAR.

Non-allergic rhinitis (NAR) is a heterogeneous disease, characterized by nasal hyperreactivity that results in typical symptoms due to irritation, such as rhinorrhoea and sneezing, and/or due to vasodilatation, such as obstruction. The diagnosis of NAR is based on persistent symptoms throughout the year after exclusion of infection, any anatomical or medical disorder, and absence of serum IgE specific to relevant aeroallergens (1-4). The aetiology of NAR is largely unknown for a majority of about 75–80% of the patients, and NAR is classified also as idiopathic or vasomotor rhinitis. This high percentage of idiopathic aetiology is, at least in part, due to the fact that nasal cytology is very rarely performed. Indeed, nasal cytology just allows to recognize and identify the different NAR

types on the basis of the particular inflammatory cell infiltrate (5). In this regard, a particular type of NAR is characterized by a distinct inflammatory cell infiltrate by eosinophils (i.e. non-allergic rhinitis with eosinophils, NARES). NARES is characterized by a profound nasal eosinophilia (>20% of the cells present in the mucosa), not associated with allergic disease (6). However, it is more frequent to detect NAR patients without a predominant cell type.

The treatment of NAR is still debated, even though different types of drugs are employed, including intranasal corticosteroids and antihistamines (7). Intranasal corticosteroids may be frequently effective as nasal inflammation represents the pathogenic basis for NAR. In this regard, flunisolide is a well-known intranasal corticosteroid molecule which

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has been very effective in the treatment of allergic rhinitis for more than 30 years (8-9). However, there are only two studies that have investigated its role in NAR treatment (10-11), but the first investigated patients with NARES, the second considered only eosinophilic infiltrate. For this reason, there is no study that investigated the effects of flunisolide on nasal cytology in patients with idiopathic NAR.

Therefore, the present study is aimed at evaluating the effect of the use of intranasal flunisolide in patients with NAR, considering both clinical and cytological parameters.

MATERIALS AND METHODS

Study population

Sixty patients, aged between 21 and 63 years (mean age 42.8 years), 39 males and 21 females, were recruited from two hospitals in Naples with the complaints of chronic nasal symptoms, including sneezing, rhinorrhea, and obstruction. Patients were included in the study if having the diagnosis of NAR. The diagnosis of NAR was made on the basis of a history of nasal symptoms (including sneezing, rhinorrhea, and nasal obstruction typically dependent on exposure to triggers such as odors, irritants, weather changes), presence of inflammatory cells on nasal smear, and negative skin prick test according to validated criteria (2-3).

Subjects were not included in the study if suffering from: acute or chronic upper respiratory infections, anatomic nasal defects (i.e. septum deviation), documented sensitization, using intranasal or oral corticosteroids, nasal or oral decongestants, antileukotrienes, and intranasal or oral antihistamines during the previous 4 weeks, or had a history of chronic epistaxis, immunodeficiency, or hypersensitivity to flunisolide.

Allergy was excluded by the absence of sensitization to the most common classes of aeroallergens by performing skin prick tests which were carried out according to the European Academy of Allergy and Clinical Immunology: sensitization was considered when the wheal diameter was equal or greater than 3 mm (12). The allergen panel consisted of the following: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria judaica*, birch, hazel tree, olive tree, cypress, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix; the concentration of allergen extracts was 100 I.R./mL* (Immunologic Reactivity) (Stallergenes, Milan, Italy).

Informed consent for participation in the study was obtained from the patients. The study was approved by the Review Board Committees.

Study design

The study was single blind, randomised, and controlled. All patients enrolled in the study were individually randomised to receive either 8 weeks of intranasal flunisolide nasal spray or isotonic saline solution with a ratio 1:1. Both the active drug and the saline solution were dispensed by the Rinowash nebuliser.

As modern therapeutic strategies involve the use of a device able to administer a correct aerosol therapy, Rinowash is a device specifically designed to administer a correct endonasal therapy, and proves particularly effective in the treatment of the upper respiratory ways (URW). Rinowash selectively arrives at the osteomeatal complex and the rhino-pharynx thanks to the dimension of the nebulized particles (13). The mass median aerodynamic diameter (MMAD) of the particles is greater than 10 micron, in accordance with the European Respiratory Society Guidelines.

At the first visit, flunisolide or saline solution was randomly prescribed to patients. Physicians carrying out the visits were blinded to whether patients assumed or not active drugs. During the 8-week study, patients dispensed 2 mL of flunisolide (0.5 mg/mL) or 2 mL of saline solution twice daily.

Evaluation and patient management

Initial assessment of each patient upon entering the study (T1) included the following: history and physical examination, skin prick test, symptom assessment score, fiberoptic endoscopy to mainly evaluate turbinate size, and nasal cytology. Sequent assessment was made at 8 weeks (T2), performing nasal endoscopy, symptom score assessment, and nasal cytology.

Nasal symptoms were assessed by using a four-point score (0= absent, 1= light, 2= moderate, 3= severe) as previously extensively described (14). Nasal itching, sneezing, rhinorrhea, and nasal obstruction were considered: the sum of these symptoms was calculated for each patient as Total Symptom Score.

Turbinate hypertrophy degree was assessed during nasal endoscopy. A validate four point score was considered (15). Briefly, during endoscopy, color 35-mm transparencies were taken with the patient in quiet nasal respiration. Photographs were taken of both left and right anterior nasal *fossae* using an Olympus OM-2 camera adapted to the rhinoscope. The turbinates size degree was considered on the basis of the distance between the medial wall of the inferior turbinate and the lateral wall of the *septum*: 0 = distance > 10 mm, 1 = distance < 10 mm and > 5 mm, 2 = < 5 mm, 3 = 0 mm.

Nasal cytology was performed as previously reported in detail (16). Briefly: cytological samples were obtained by scraping with a Rhino-Probe™. The samples were

collected from the medial portion of the inferior middle turbinate. After fixing with absolute alcohol for 3 minutes, the samples were stained using the May-Grünwald-Giemsa and read by light microscope. Data were expressed as percentage of inflammatory cells on total recovered cells. Any adverse event was recorded.

Statistical analysis and data definitions

Three major outcomes of interest were considered: 1) the difference in the decline in rhinitis nasal scores, 2) turbinate hypertrophy, 3) nasal cytology rate from baseline between the two groups to T2.

Descriptive statistics were firstly performed and quantitative parameters were reported as means and standard deviations (SD). Qualitative data were reported as frequencies and percentages. Comparison of qualitative data among the two groups of patients was made by the chi-square test (or by the Fisher's Exact test in case of expected frequencies less than five).

The Mann-Whitney test was used as a nonparametric counterpart. Quantitative variables (nasal scores, turbinate hypertrophy, nasal cytology) for paired data were compared using the Wilcoxon test. Linear correlation between pairs of quantitative variables was evaluated by Spearman's correlation coefficient (r). For the purpose of the analysis, correlation coefficients >0.8 were considered as very strong, from 0.6 to 0.79 were considered as strong, from 0.4 to 0.59 were considered as moderate, from 0.2 to 0.39 were considered as weak, and <0.2 were considered as very weak.

For the analysis, a $p < 0.05$ was considered statistically significant. The mean $\pm$ SD and SE was used in the graphs. A statistical software program (StatSoft Italia s.r.l. 2005. Statistica, Vigonza, Italy) was used for all the analyses.

RESULTS

All patients enrolled in the study completed the 8-week trial. No clinically relevant adverse events were reported in both groups. Baseline demographic and clinical characteristics were reported in Table I for both groups. The two groups were well matched for all considered parameters ($p = \text{n.s.}$).

Intragroup analysis

Saline solution treatment (Group A) did not induce any significant change on all considered parameters as reported in Table II. Particularly, nasal symptoms, turbinates size, and inflammatory cells were not affected by saline solution treatment as shown in Figure 1. Intranasal flunisolide treatment (Group B) was able of significantly reduce: the nasal score ($p < 0.0036$), turbinates size ($p < 0.0015$), and inflammatory cell counts ($p < 0.001$ for all inflammatory cell types) as reported in Table II and in Fig.1.

Intergroup analysis

Intranasal flunisolide induced lower symptom severity than saline ($p < 0.00001$), turbinates size ($p < 0.00001$) and inflammation ($p < 0.00001$ for all cell types) as reported in Table III. No clinically relevant adverse events were reported in either group.

Relationships

At baseline, symptom score was strongly related with turbinates size ($r=0.63$) as reported

Table I. Baseline demographic and clinical characteristic of the 60 evaluated patients.

Characteristic	Group A (30 pts)	Group B (30 pts)	P value
Gender- males, N (%)	18 (60)	21 (70)	N.S.†
Age (years), mean $\pm$ S.D.	33.2 $\pm$ 8.6	32.1 $\pm$ 9.4	N.S. *
Nasal Score, mean $\pm$ S.D	8.9 $\pm$ 2	8.3 $\pm$ 1.8	N.S. *
Turbinate hypertrophy, mean $\pm$ S.D.	2.1 $\pm$ 0.7	2 $\pm$ 0.6	N.S. *
Nasal cytology, mean $\pm$ S.D			
Neutrophil	1.5 $\pm$ 0.5	1.7 $\pm$ 0.4	N.S. *
Eosinophil	1.3 $\pm$ 0.7	1 $\pm$ 0.7	N.S. *
lymphocyte	0.9 $\pm$ 0.7	1 $\pm$ 0.6	N.S. *

The percentages in round brackets are calculated over the total number of subjects reported at the top of column. †: Chi-squared test. *: Mann-Whitney U test.

Table II. Intragroup analysis of clinical characteristic of the two evaluated patient Groups. (Group A treated with saline solution; Group B treated with intranasal flunisolide) at visit 1 and visit 2.

GROUP A

Characteristic	Visit 1	Visit 2	P value
Nasal Score, mean $\pm$ S.D.	8.9 $\pm$ 2	9.7 $\pm$ 2	N.S.**
Turbinate hypertrophy, mean $\pm$ S.D.	2.1 $\pm$ 0.7	2 $\pm$ 0.7	N.S.**
Nasal cytology, mean $\pm$ S.D.			
Neutrophil	1.5 $\pm$ 0.5	1.6 $\pm$ 0.4	N.S.**
Eosinophil	1.3 $\pm$ 0.7	1.2 $\pm$ 0.5	N.S.**
lymphocyte	0.9 $\pm$ 0.7	0.9 $\pm$ 0.6	N.S.**

** Wilcoxon test

GROUP B

Characteristic	Visit 1	Visit 2	P value
Nasal Score, mean $\pm$ S.D.	8.3 $\pm$ 1.8	3.4 $\pm$ 1.1	0.0036**
Turbinate hypertrophy, mean $\pm$ S.D.	2 $\pm$ 0.6	0.8 $\pm$ 0.7	0.0015**
Nasal cytology, mean $\pm$ S.D.			
Neutrophil	1.7 $\pm$ 0.4	1 $\pm$ 0.4	<0.001**
Eosinophil	1 $\pm$ 0.7	0.2 $\pm$ 0.4	<0.001**
lymphocyte	1 $\pm$ 0.6	0.3 $\pm$ 0.4	<0.001**

** Wilcoxon test

Table III. Intergroup analysis of considered parameters between Group A and Group B at visit 2.

Characteristic	Group A	Group B	P value
Nasal Score, mean $\pm$ S.D.	9.7 $\pm$ 2	3.4 $\pm$ 1.1	< 0.00001*
Turbinate hypertrophy, mean $\pm$ S.D.	2 $\pm$ 0.7	0.8 $\pm$ 0.7	<0.0001*
Nasal cytology, mean $\pm$ S.D.			
Neutrophil	1.6 $\pm$ 0.4	1 $\pm$ 0.4	<0.0001*
Eosinophil	1.2 $\pm$ 0.5	0.2 $\pm$ 0.4	<0.0001*
lymphocyte	0.9 $\pm$ 0.6	0.3 $\pm$ 0.4	<0.0001*

*: Mann-Whitney U test

in Fig. 2. In addition, neutrophil count showed a strong relationship with symptom severity ($r=0.65$) as shown in Fig. 2, whereas eosinophils and lymphocytes were weakly related with symptom score ($r= 0.34$ and 0.39 respectively).

After treatment, symptom severity was

moderately related with turbinates size ($r= 0.54$) as shown in Fig. 3. In addition, neutrophils count moderately correlated with symptom severity ($r= 0.48$) as reported in Fig. 3. Eosinophils and lymphocytes weakly related with symptoms score ($r= 0.35$ and 0.31 respectively).

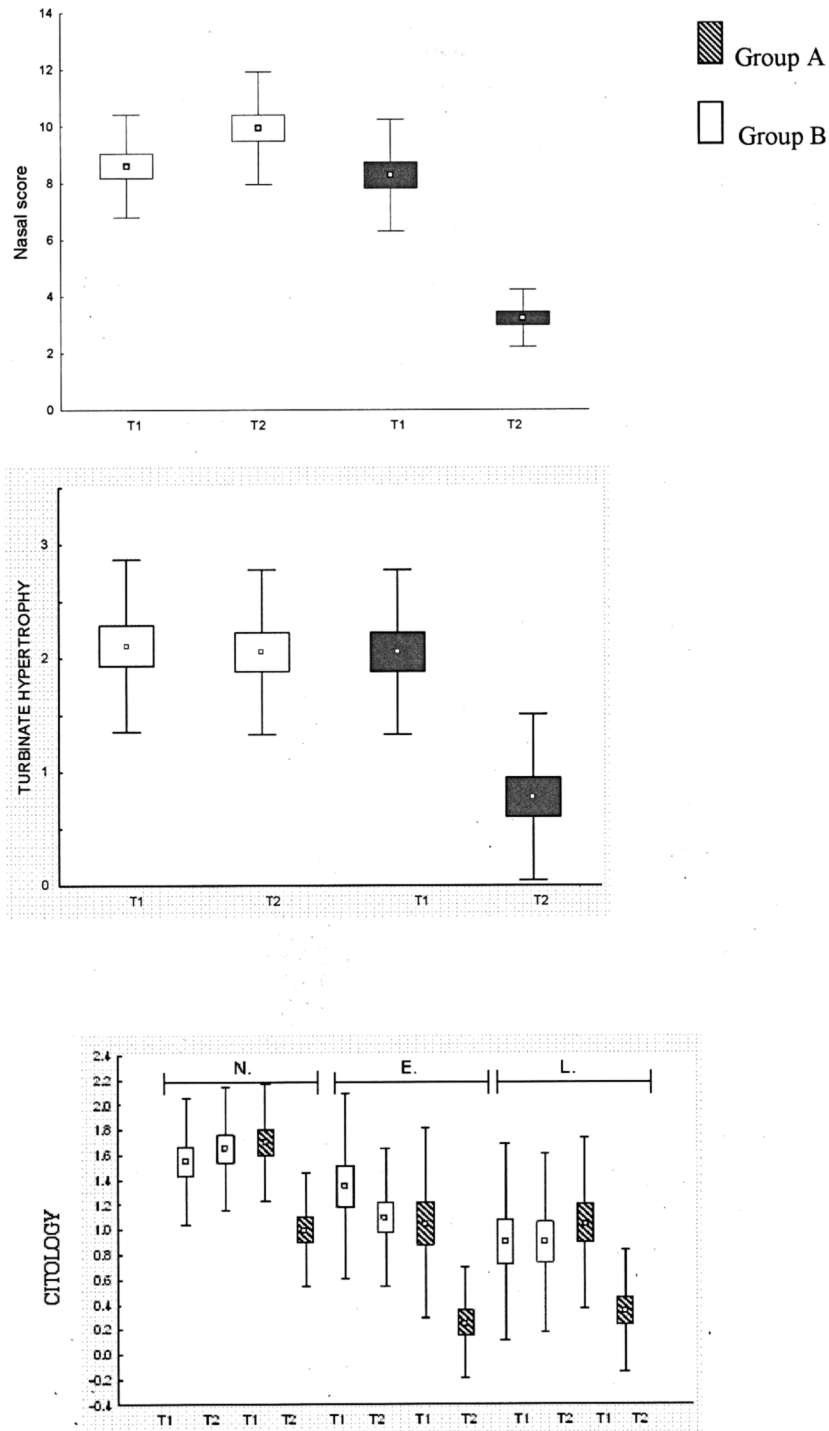


Fig. 1. Upper quadrant = mean $\pm$ S.D. of Nasal Score at baseline (T1) and after treatment (T2) in Group A and Group B; middle quadrant = mean $\pm$ S.D. of Turbinate Size at baseline (T1) and after treatment (T2) in Group A and Group B; lower quadrant = mean $\pm$ S.D. of Nasal Cytology (N: neutrophils, E: eosinophils, L: lymphocytes) at baseline (T1) and after treatment (T2) in Group A and Group B.

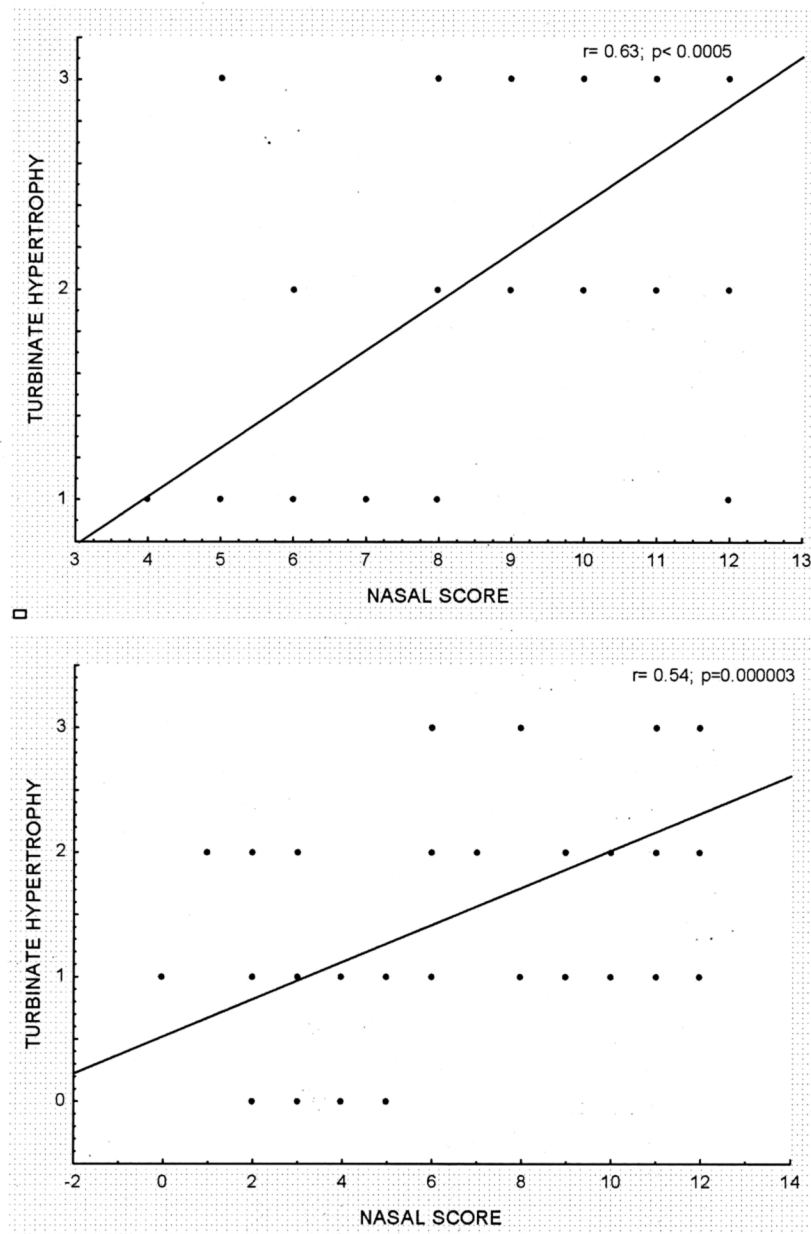


Fig. 2. Upper quadrant = relationship between turbinate size and nasal score at baseline; lower quadrant = relationship between turbinate size and nasal score after treatment.

DISCUSSION

Rhinitis is a very common disease which may affect all subjects. Rhinitis may be classified on the basis of aetiology: for example as infectious rhinitis (such as common cold), hormonal rhinitis

(for example during pregnancy or thyroid disorder), occupational, etc. However, a common cause of chronic rhinitis is allergy, even though there are many patients suffering from chronic nasal complaints who have no allergen-specific IgE. Therefore, the term of non allergic rhinitis (NAR) is usually considered

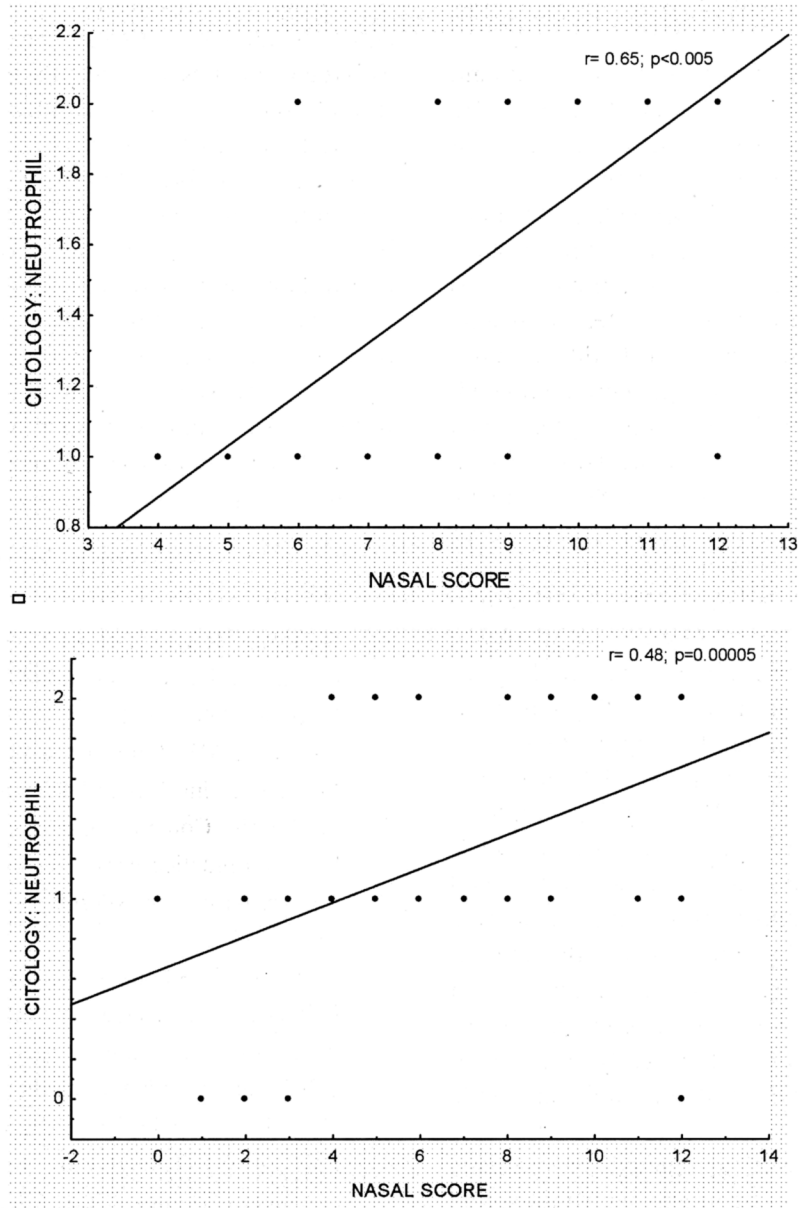


Fig. 3. Upper quadrant = relationship between neutrophils and nasal score at baseline; lower quadrant = relationship between neutrophils and nasal score after treatment.

for defining these patients. Moreover, NAR may be classified considering the predominant type of infiltrating inflammatory cells. The most famous NAR is NARES, such as characterized by relevant eosinophilic infiltrate. However, most NAR patients do not show any relevant inflammatory type; these

patients are labelled as suffering from the so called idiopathic or vasomotor rhinitis.

The treatment of NAR is still debated, even though symptomatic drugs are commonly used, including intranasal corticosteroids and antihistamines (7). The rational of prescribing corticosteroids is based on the

concept that NAR is sustained by an inflammatory process.

Intranasal flunisolide is an effective compound which has been prescribed for more than 30 years (8-9). However, only two studies have been aimed at investigating its efficacy in NAR patients.

A study evaluated 90 patients with idiopathic non-allergic rhinitis: they were divided into three groups. Silver nitrate was given to Group I, flunisolide to Group II, and placebo to Group III. Healing results according to symptoms, physical findings, nasal smear findings and biopsy findings were compared. Improvement was noticed in symptoms (rhinorrhea 93%, sneezing 89%, nasal congestion 80%), physical findings (color of mucosa 89%, concha hypertrophy 87%, rhinorrhea 82%), nasal smear findings (94%) and biopsy findings (epithelium 76%, basal membrane 80%, edema 84%, eosinophilia 95%, inflammation 87%) in Group I. Recurrence was observed in symptoms and physical findings of 30% of the patients in Group I during the 6 months-follow-up period. In Group II, improvement was noticed in symptoms (rhinorrhea 73%, sneezing 70%, nasal congestion 61%), physical findings (color of mucosa 72%, concha hypertrophy 69%, rhinorrhea 62%), nasal smear findings (87%) and biopsy findings (epithelium 67%, basal membrane 63%, edema 70%, eosinophilia 77%, inflammation 70%). But symptoms recurred in all patients in approximately 1-3 months after completion of treatment. There was a statistically significant difference between silver treatment and flunisolide or placebo treatment.

The other study was conducted on patients with NARES comparing treatment with flunisolide alone or flunisolide associated with loratadine (an antihistamine): intranasal flunisolide was able of reducing all considered parameters.

However, neither study analytically considered inflammatory cell types and turbinate size. Therefore, this study was performed to add new information on flunisolide efficacy in treating patients with NAR.

The results demonstrate that intranasal flunisolide significantly reduced the severity of nasal symptoms, the size of turbinates, and inflammatory cells. This effect may be due to a general anti-inflammatory action in respiratory upper airway.

Moreover, this study provides evidence that there

is a strong relationship between symptom severity and turbinate size. This fact is easily understandable as large turbinates significantly impair nasal airflow. In addition, the degree of inflammation, calculated on the basis of cell count, is related with symptom severity. Therefore, flunisolide is effective on symptom control because it is capable of reducing both inflammatory infiltrate and turbinate size by anti-inflammatory activity.

In conclusion, this study demonstrates that an 8-week treatment with intranasal flunisolide is significantly associated with reduction of symptoms, turbinate size and inflammation in patients with NAR. Thus, intranasal flunisolide might be a therapeutic option for NAR.

REFERENCES

1. Settipane RA, Charnock DR. Epidemiology of rhinitis: allergic and nonallergic. *Clin Allergy Immunol* 2007; 19:23-9.
2. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J. Diagnosis and management of rhinitis. Complete guidelines of the Joint Task Force on practice parameter in allergy, asthma, and immunology. *Ann Allergy Asthma Immunol* 1998; 81:478-44.
3. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy* 2008; 63:8-160.
4. Fokkens WJ. Thoughts on the pathophysiology of nonallergic rhinitis. *Curr Allergy Asthma Reports* 2002; 2:203-11.
5. Gelardi M, Cassano P, Cassano M, Fiorella ML. Nasal cytology: description of a hyperchromatic supranuclear stria as a possible marker for the anatomical and functional integrity of the ciliated cell. *Am J Rhinol* 2003; 17:263-9.
6. Ellis AK, Keith PK. Nonallergic rhinitis with eosinophilia syndrome and related disorders. *Clin Allergy Immunol* 2007; 19:87-94.
7. Ciprandi G. Treatment of nonallergic perennial rhinitis. *Allergy* 2004; 56:16-23.
8. Pakes GE, Brogden RN, Heel RD, Speight TM, Avery

- GS. Flunisolide: a review of its pharmacological properties and therapeutic efficacy in rhinitis. *Drugs* 1980; 19:397-11.
9. Sy RK. Flunisolide intranasal spray in the treatment of perennial rhinitis. *Arch Otolaryngol* 1979; 105: 649-53.
10. Purello-D'Ambrosio F, Isola S, Ricciardi L, Gangemi S, Barresi L, Bagnato GF. A controlled study on the effectiveness of loratadine in combination with flunisolide in the treatment of nonallergic rhinitis with eosinophilia (NARES). *Clin Exp Allergy* 1999; 2:1143-7.
11. Erhan E, Külahlı I, Kandemir O, Cemiloglu R, Yigitbasi OG, Cüreoglu S. Comparison of topical silver nitrate and flunisolide treatment in patients with idiopathic non-allergic rhinitis. *Tokai J Exp Clin Med* 1996; 21:103-11.
12. Dreborg S. EAACI Subcommittee on Skin Tests. Skin tests used in type I allergy testing. *Position Paper. Allergy* 1989; 44:22-67.
13. Varricchio A, Tortoriello G, Papasso M, et al. Prevention of surgery in children with Adenoidal Hypertrophy treated with intranasal flunisolide: a 12-month follow-up. *J Biol Reg* 2009; 23:95-101.
14. Ciprandi G, Cirillo I, Vizzaccaro A, Milanese M, Tosca MA. Nasal obstruction in patients with seasonal allergic rhinitis: relationships between allergic inflammation and nasal airflow. *Int Arch Allergy Immunol* 2004; 134:34-8.
15. Friedman M, Tanyeri H, Landsberg R, Caldarelli M. A safe, alternative technique for inferior turbinate reduction. *Laryngoscope* 1999; 109:1934-7.
16. Gelardi M, Fiorella R, Fiorella ML, Russo C, Soleti P, Ciprandi G. Nasal-sinus polyposis: clinical-cytological grading and prognostic index of relapse. *J Biol Reg* 2009; 23:181-8.