

Evaluation of Performance and Tolerability of Nebulized Hyaluronic Acid Nasal Hypertonic Solution in the Treatment of Chronic Rhinosinusitis

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Abstract

Background: Nasal solutions are part of the recommended therapy of chronic rhinosinusitis (CRS). Formulations containing hyaluronic acid (HA) may represent a promising topical treatment in CRS patients in light of the anti-inflammatory and protective effect of HA on the sinonasal mucosa.

Objective: Primary aim was to evaluate the performance of a new nebulized HA nasal hypertonic solution in the relief of symptoms of CRS. Secondly, evaluation of symptoms improvement, endoscopic nasal findings, and safety profile were assessed.

Methods: A monocenter, single arm, not controlled, premarket clinical trial on a new nasal solution containing HA was performed. All the included patients had a history of previously diagnosed or recurrent CRS or they had received a clinical diagnosis of CRS defined, according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Each patient was evaluated on 3 visits. Endoscopic nasal examination and Nasal Obstruction Symptom Evaluation Instrument questionnaire filling were performed during each visit. Patients' adherence to treatment and overall satisfaction, patients' and investigator's global evaluation of performance, and safety parameters were also assessed.

Results: Eighty patients were enrolled. The use of the investigated HA nasal solution revealed to be significantly effective in the relief of symptoms of CRS. According to daily patients' diaries, several signs and symptoms significantly improved after therapy. The comparison between endoscopic assessments before and after treatment confirmed improvement of the condition in at least 75% of patients. Seventy-four percent of the patients were quite or very satisfied with the treatment and 80% reported an improvement. The investigator's global assessment of performance was in agreement with this view, as more than 80% of the patients were considered clinically improved.

Conclusions: The use of the investigated new nebulized HA nasal hypertonic solution is an effective and safe the treatment of CRS.

Keywords

hyaluronic acid, Nasal Obstruction Symptom Evaluation Instrument score, nasal washes, nasal solution, topical treatment, nebulized solution, chronic rhinosinusitis, symptoms, safety profile, endoscopic assessment

Introduction

Chronic rhinosinusitis (CRS) is a common condition characterized by mucosal inflammation of the nasal cavity and paranasal sinuses, associated with nasal congestion or obstruction, facial pain, and olfactory disturbance, persisting longer than 12 weeks. CRS is not a disabling disease; however, it is one of the most

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common causes of absence from work and for visits to a family doctor's office. Diagnosis of CRS is primarily based on symptoms and then confirmed by endoscopy and/or computed tomography.¹

The goals of medical therapy for CRS are to reduce mucosal edema, promote sinus drainage, and eradicate infections that may be present. This often requires a combination of topical or oral corticosteroids, antibiotics, and nasal saline irrigation.²

Hyaluronan, also known as hyaluronic acid (HA), is a nonsulfate glycosaminoglycan formed by a chain of dimers each constituted by a D-glucuronic acid molecule and a D-N-acetylglucosamine.³ HA is one of the main constituents of all connective matrices and many organic liquids and is widely distributed in the body. HA is found in human respiratory epithelial cells and serous cells in submucosal glands and accounts for approximately 80% of uronic acids in human nasal secretions.⁴

There is increasing evidence that aerosolized exogenous HA may be useful for the prevention of recurrent CRS and may have an anti-inflammatory and protective effect in some respiratory conditions.⁵ The nebulization permits integration in the mucosa of the entire respiratory tract, performing the regulation functions of hydration and mucociliary clearance useful for inflammatory or allergic reactions.⁶

Topical HA could be a new CRS treatment strategy that can minimize symptoms, promote recovery, and prevent exacerbations.^{7,8}

The RCF 15122 (Ricerfarma Srl—Milano) is a novel medical device for the treatment of CRS symptoms that combines the protective, hydrating, anti-edema, and anti-irritant properties of the HA with emollient and moisturizing properties of the Aloe Vera, together with a slight osmotic effect of the sodium chloride that helps thinning of the mucus and facilitate its elimination. It is a promising product that could help limiting the use of vasoconstrictor and corticosteroid-based treatments in CRS patients.

The aim of present paper would be to evaluate the performance and safety of the new RCF 15122 medical device (RhinoialTM) on a cohort of 80 patients complaining symptoms of CRS.

Materials and Methods

A monocenter, single arm, not controlled, premarket clinical trial on the medical device RhinoialTM was performed.

Medical Device

RhinoialTM is a short-term use, Class IIa Medical Device, manufactured by Ricerfarma Srl, Milano, Italy. It is a nasal solution with wetting characteristics

and secondary mucosa-protecting activities due to the action of high-molecular-weight HA and decongestant activities due to the presence of (1) sodium chloride which, by drawing water from the tissues, reduces mucosal swelling, thin the mucus facilitating its elimination, thus clearing the nasal airways; (2) aloe extract, which reduces local irritation caused by mucosal swelling.

When applied twice a day in each nostril, to the target areas, RhinoialTM forms a protective film and exercises its lenitive, anti-irritant, anti-inflammatory, and protective action on the nasal mucosa with consequent anti-edematous and decongestive action. The product was labeled as experimental treatment in accordance with Good Manufacturing Practice (GMP, Annex 13).

Inclusion and Exclusion Criteria

In this clinical investigation, 80 subjects aged ≥ 18 years were enrolled. All the patients had a history of previously diagnosed or recurrent CRS that required antibiotic therapy as judged by the investigator; or they had received a clinical diagnosis of CRS defined, according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012, as the presence for ≥ 12 weeks of 2 or more symptoms, 1 of which should be either (i) nasal blockage/obstruction/congestion or (ii) nasal discharge (anterior/posterior nasal drip), with or without presence of (iii) facial pain/pressure or (iv) reduction or loss of smell.⁹

Patients who had undergone previous sinus-nasal surgery in the last 12 months before study inclusion, with history or presence of benign and malignant tumors of the nasal cavity, history of recurrent epistaxis, coagulation disorders, previous head and neck radiotherapy, major psychiatric diseases likely to require or under treatment with antidepressant drugs, and evidence or history of chronic bacterial rhinosinusitis or of congenital or acquired immunodepression, were excluded from the study. Patients having used sinus lavage within the previous 7 days or systemic corticosteroids, immunosuppressive agents or intranasal corticosteroids within the past 8 weeks were also excluded. The use of decongestants, antihistamines, mucolytics, sodium cromoglycate, analgesics (including non-steroidal anti-inflammatory drugs [NSAIDs]), antibiotics, immunosuppressant drugs, and other nasal douche in addition to that scheduled by protocol within the past 2 weeks was a further criterion not to enroll such patients in the study. During the investigation, none of these medications was used.

General physical examination was performed on all enrolled patients, and it was considered positive when at least 1 clinical finding was identified.

Clinical investigation methods and endpoints. Patients were instructed to use RhinoialTM twice daily, the first

application in the morning and the second in the evening before bedtime, for 20 consecutive days.

Two puffs (each puff corresponding to 140 μ L) per nostril had to be administered at each application.

Each patient was assessed on 3 visits:

- visit 1: screening according to inclusion and exclusion criteria and baseline-start treatment (day 0);
- visit 2 (day 10 $\pm$ 2): follow-up; and
- visit 3 (day 20 $\pm$ 2): end of study

Endoscopic nasal examination and I-NOSE (Nasal Obstruction Symptom Evaluation Instrument) questionnaire filling were performed during each visit.¹⁰

Primary aim was to evaluate the performance of the investigated nebulized HA nasal hypertonic solution in the relief of nasal and sinus symptoms of CRS. This was assessed by change from baseline in the I-NOSE questionnaire score, at each postbaseline time point.

To assess performance parameters, evaluation of symptoms improvement was assessed by change from baseline of score of each individual sign and symptom as reported by the patient in the daily patient's diary (nasal blockage or congestion, nasal drainage/rhinorrhea, facial pain or pressure, facial congestion or fullness, nasal dryness, nasal stinging, sneezing, and change in taste or smell). The rating was from 0 (not a problem) to 4 (severe problem).

Change from baseline in findings at the endoscopic nasal examination in terms of middle turbinate edema and nasal secretions was scored at the baseline (visit 1) and end of treatment (visit 3) visits by means of a 0 to 3 scale, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

Patients' adherence to treatment with the medical device was evaluated by counting the number of units dispensed to patients and the number of unused units returned by patients at the final visit (according to the extent of exposure to treatment), considering that each patient had 1 puff per nostril only (half treatment) in the first and last day of treatment. Those patients who had 2 puffs in the first and/or last day of treatment were considered as compliant patients for data analysis.

Patients' and investigator's global evaluation of performance of the nebulized HA nasal solution treatment was performed by means of the 7-item Clinical Global Impression scale (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse at the end of the study compared to baseline).

Patients' evaluation of overall satisfaction with treatment (which takes into account performance, tolerability, convenience and ease of use) was assessed by means of a 0 to 4 scale, where 4 = very much satisfied,

3 = satisfied, 2 = neither satisfied nor dissatisfied, 1 = dissatisfied, and 0 = very much dissatisfied.

Regarding safety parameters, the number and type of adverse events (AEs) occurring during the study (seriousness, severity, and relation to study treatment) were registered. Local tolerability at the site of administration (eg, nasal burning, irritation, congestion) was also investigated.

Statistical Analysis

Descriptive statistical analysis of all relevant variables was performed. Continuous variables were summarized by the number of patients, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized by the number (N) and the proportion of patients (%). Where appropriate, 95% confidence intervals for the target variables were estimated.

The significance level of statistical tests was set at 0.05. The statistical analysis was performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, North Carolina, USA).

Ethical Consideration

The study was conducted in compliance with the current version of the Declaration of Helsinki, with the clinical investigation plan, the ISO 14155:2012, the Italian laws in force, and the principles of the Good Clinical Practice.

Informed consent was obtained from each participant in the study in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) Guidelines and the Declaration of Helsinki.

The Ethics Committee (Comitato Etico di Area Vasta Emilia Nord of the Clinical Site [Struttura Complessa di Otorinolaringoiatria—Azienda Ospedaliero-Universitaria di Modena, Modena, Italy]) and the Italian Ministry of Health approved this clinical investigation.

Results

Study Population

Eighty subjects were enrolled in this clinical trial. The first subject was enrolled on March 5, 2018 and the last subject on September 25, 2018. One subject dropped out soon after visit 1 due to an AE (biliary colic). Figure 1 shows the patients' disposition at each visit. None of the patients included suffered from asthma or aspirin-exacerbated respiratory disease at the time of enrollment in this study.

The male:female ratio was nearly 1:1 (41 men vs 39 women). Mean age at informed consent visit was 56 years old (range: 18–94). All subjects belonged to the Caucasian ethnic group.

Thirteen patients were current smokers (16.25%) and 15 former smokers (18.75%).

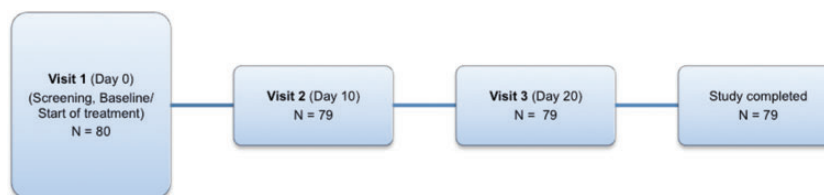


Figure 1. Patients' disposition.

Table 1. Information on Patients' History and Physical Examination at Time of Enrollment.

Medical history	
Hypertension	18
Diabetes	2
Hypothyroidism	1
Previous transient ischemic attack	1
Surgical history	
Appendectomy	8
Cholecystectomy	2
Thyroidectomy	2
Adenoidectomy/tonsillectomy	10
Prostatectomy	1
Mastectomy	1
Physical examination	
Palpable thyroid gland	3
Palpable neck lymph nodes	3
Musculo-skeletal pain	5
Heart murmur	1
Chronic venous insufficiency of lower limbs	3

Twenty-two patients (27.5%) had positive medical history, while 24 patients (30%) had undergone surgical treatment for diseases outside the nose and paranasal sinuses district before enrollment. Physical examination was positive in 15 patients (18.75%), as reported in Table 1.

Prior or concomitant medications were used by 26 patients (32.50%). Only 1 patient had undergone endoscopic sinus surgery for chronic maxillary sinusitis 5 years before study enrollment.

Compliance with the scheduled visits was high (99%). According to the patient diaries, the mean compliance with device administration was 98.47% (standard deviation 3.83, minimum–maximum: 72.22–100).

Excluding the drop-out patient, only 1 subject had a global compliance lower than 80%, considering the first and second diaries.

Primary Endpoints: Performance Analysis

The primary assessment of the performance of RhinoialTM was based on the changes from baseline in

the I-NOSE score at each postbaseline time point, as shown in Figure 2.

The change with respect to baseline was statistically significant ($P < .001$) both at visit 2 (−2.95; 95% confidence interval [CI] −3.74/−2.16) and at visit 3 (−6.77; 95% CI −7.85/−5.66). In analyzing each item of I-NOSE separately, the changes compared to baseline were always statistically significant.

Secondary Endpoints: Efficacy Variables

According to the analysis of daily patients' diary on sign and symptoms, nasal blockage and nasal congestion significantly improved ($P < .01$) between day 1 and day 20 (Figure 3). Nineteen patients had no nasal blockage at day 20 versus only 9 at day 1. Twenty-two patients had no nasal congestion at day 20 versus only 10 at day 1.

Nasal drainage and rhinorrhea also significantly improved ($P < .01$) between day 1 and day 20 (Figure 4). Specifically, 34 patients had no nasal drainage at day 20 versus 18 at day 1, while 45 patients had no nasal drainage at day 20 versus 33 at day 1.

Facial pain and facial congestion were rarely reported, and no significant improvement was detectable. The improvement in nasal dryness was not statistically significant. Nasal stinging significantly improved ($P < .05$) between day 1 and day 20. Fifty-eight patients had no nasal stinging at day 20 versus 47 at day 1. Sneezing significantly improved ($P < .01$) between day 1 and day 20, and 45 patients reported no sneezing at day 20 versus 30 at day 1. The improvement in change in smell between day 1 and day 20 was statistically significant ($P < .05$). About 87% of the patients did not reported a change in taste at day 1 and no improvement was detectable.

Middle turbinate edema and nasal secretion at nasal endoscopic evaluation significantly improved ($P < .001$) in at least 75% of patients between visit 1 and visit 3 (Figure 5(A) and (B)). Seventy-four percent of the patients were quite or very satisfied with the treatment and 80% reported an improvement, considering their condition was between slightly and much improved. The investigator's global assessment of performance was in agreement with this view, as more than 80% of the patients were considered clinically improved.

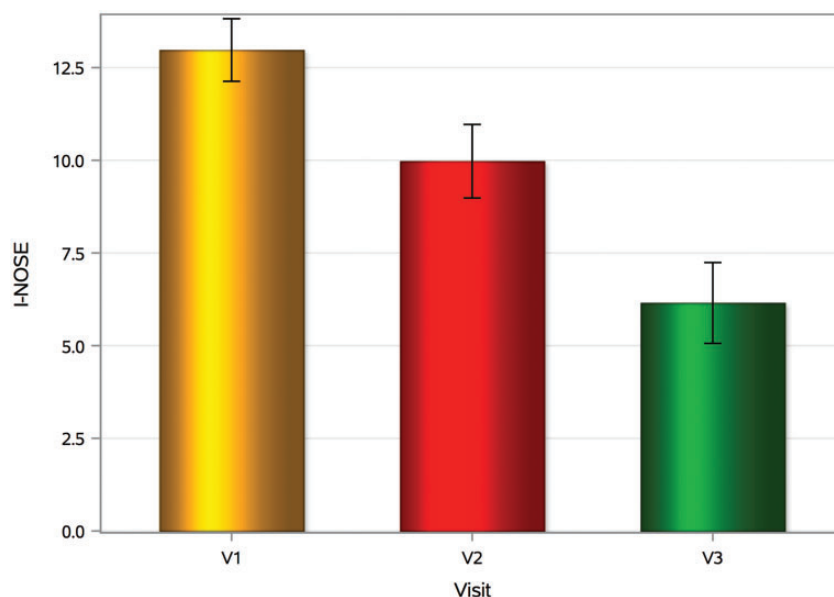


Figure 2. I-NOSE score during the study. I-NOSE, Nasal Obstruction Symptom Evaluation Instrument.

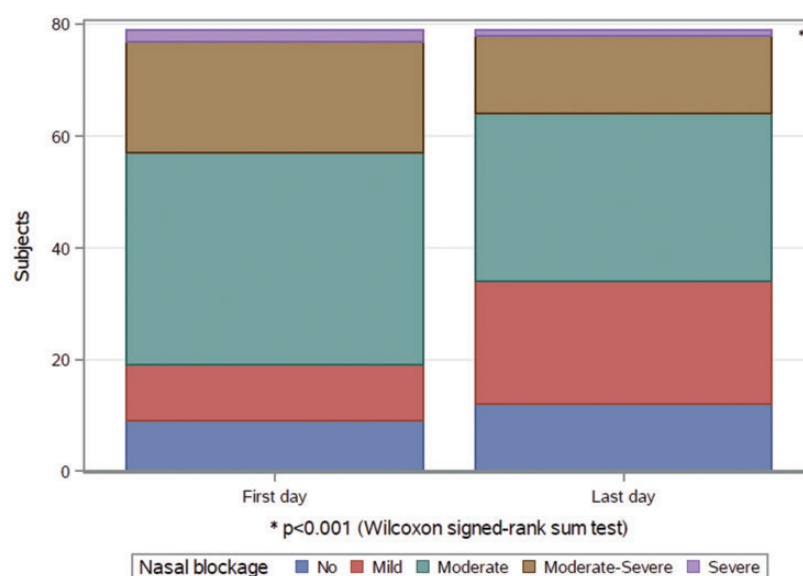


Figure 3. Nasal blockage improvement.

Secondary Endpoints: Safety Variables

The participants' safety was carefully monitored, and all events detected by the Investigator and reported by the patients were recorded and analyzed. Twenty-five events were registered so far. Fourteen patients (17.50%) experienced at least an AE each (Table 2). A serious AE occurred: patient 01-048 experienced a biliary colic, not related to the study treatment, which caused his withdrawal from the study. No symptoms related to local tolerability at the site of administration (eg, nasal burning, irritation, congestion) were reported.

Discussion

According to recent literature, CRS represents a significant disease burden among general population due to its high prevalence and relevant morbidity.¹¹

CRS is accompanied by chronic sinonasal symptoms that may lead to a worsening in quality of life (QoL) of affected patients, in such way that it has been compared (as similar or even worse) to other chronic conditions, such as heart disease and asthma. As reported by Gray et al., higher levels of patient-reported CRS symptom control are associated with better QoL, suggesting that

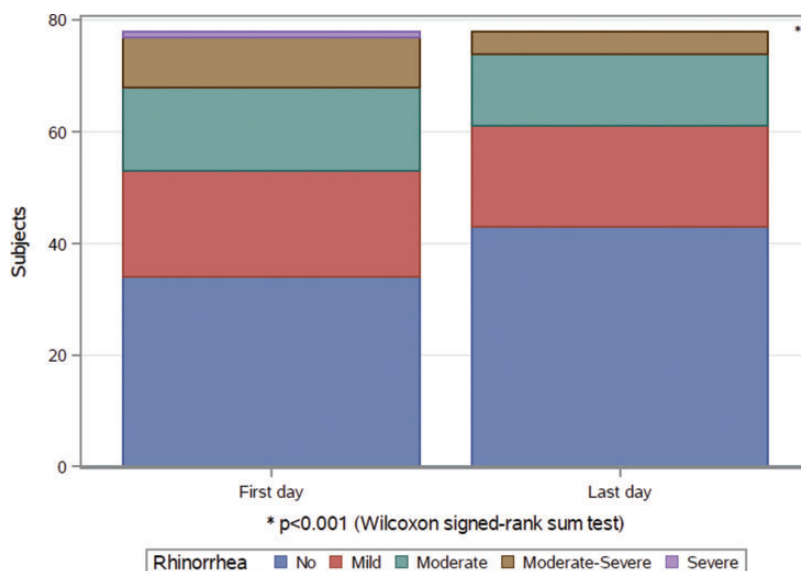


Figure 4. Rhinorrhea improvement.

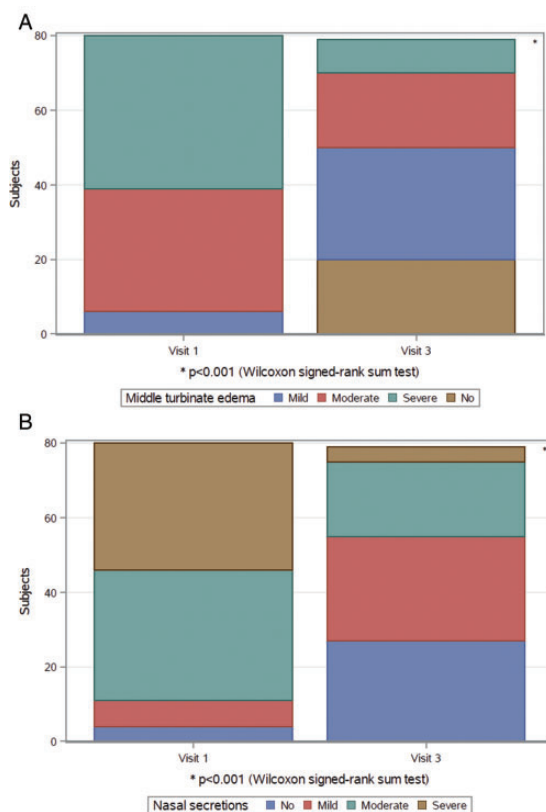


Figure 5. A, Nasal endoscopy findings during the study—middle turbinate edema. B, Nasal endoscopy findings during the study—nasal secretions.

medical actions aimed to control CRS symptoms would be relevant for improving patients' QoL.¹²

Treatment of CRS is aimed to reduce mucosal inflammation, improve sinus drainage, remove local infection,

and improve access for topical medications. Medical management is the mainstay treatment of CRS and is based on a combination of nasal saline irrigations, decongestants, nasal and systemic steroids, and courses of antibiotics when needed. Endoscopic sinus surgery is recommended in those cases where the medical treatment was unsuccessful.^{2,13,14}

Topical medical treatment represents an attractive form of drug delivery into the nasal cavity and paranasal sinuses. Indeed, topical drug delivery has several advantages: it guarantees a direct action on the site of pathology, improves the concentration of the drug at the target site, and has virtually no systemic adverse effects.¹⁴

Daily saline nasal washes are part of the recommended topical treatment of CRS.^{9,15}

Recently nasal solutions containing HA have been proposed as part of treatment of CRS. HA belongs to glycosaminoglycans and is a fundamental component of the extracellular space. Emerging data show that hyaluronan and its degradation products have an important role in the pathobiology of the respiratory tract, in particular in airway diseases with a predominant inflammatory component such as rhinosinusitis, asthma, chronic obstructive pulmonary disease, cystic fibrosis, and primary ciliary dyskinesia.

The mucociliary system is among the primary defense mechanisms of the airways, and impairment of mucociliary clearance predisposes to chronic airway infections. CRS is characterized by a marked decrease in mucociliary clearance. Recent evidences show that HA, in addition to its anti-inflammatory activity, promotes mucociliary transport and helps to prevent the recurrence of CRS suggesting a possible role for HA in diseases of the upper respiratory tract.^{7,16,17}

Table 2. Summary of Adverse Events Occurred During the Study.

System Organ Class Preferred Term	Event	Patient	Intensity Mild	Intensity Moderate	Intensity Severe	Relationship to Study Treatment
Overall	25	15	21	3	1	
Ear and labyrinth disorders	1	1				
Ear pain	1	1	1			None
Eye disorders	2	2				
Lacrimation increased	2	2	1	1		None
Gastrointestinal disorders	1	1				
Oral pain	1	1	1			None
Hepatobiliary disorders	1	1				
Biliary colic	1	1			1	None
Infections and infestations	1	1				
Skin papilloma	1	1	1			Unknown
Musculoskeletal and connective tissue disorders	2	2				
Bone pain	1	1	1			None
Neck pain	1	1	1			None
Nervous system disorders	14	8				
Dizziness	2	1	2			None
Headache	11	7	10	1		None
Migraine	1	1		1		None
Respiratory, thoracic, and mediastinal disorders	3	3				
Cough	1	1	1			None
Nasopharyngitis	2	2	2			None

In a recent study, 75 children with recurrent upper respiratory tract infections were treated with aerosolized HA (0.3% solution in normal saline) or normal saline alone.¹⁸ HA showed a great improvement of rhinitis symptoms compared with saline alone. In addition, ciliary motility resulted significantly improved in the HA group.

Also HA has been successfully tested in clinical studies for the treatment of patients who suffer from CRS and undergo surgical procedures of the nasal cavity such as septoplasty, turbinate surgery, or simple ethmoid surgery.¹⁹

Hitherto, HA has been widely used in several other branches of medicine, and neither contraindications nor interactions with drugs have been reported.^{20–22}

RhinoialTM (Ricerfarma Srl–Milano) is a novel medical device for the treatment of CRS symptoms that combines the protective, anti-irritant, and anti-inflammatory HA properties with anti-constricting, healing, and moisturizing properties of the true Aloe Vera.

Beneficial effects of this device on mucosal edema and clearance in CRS patients may be also attributable to the product's tonicity (sodium chloride concentration greater than 0.9%).^{23–25}

In view of these characteristics, RhinoialTM is a promising product that could be useful in reducing the consumption of vasoconstrictor and corticosteroid-based treatments by CRS patients, especially for attenuating the symptoms of this relevant condition. The efficacy

and safety profile of this new medical device have been assessed through the present clinical investigation.

Significant improvement of CRS symptoms as reported from the patients' themselves emerged from the analysis of changes in the I-NOSE scores from baseline to last visit. Even when considering each item of I-NOSE separately, the symptoms exhibited the same significant positive trend.

The analysis of efficacy variables still focused patient's subjective experience of CRS symptoms: according to the changes in sign and symptoms intensity as reported daily on patients' diary, an improvement between day 1 and day 20 emerged for nasal blockage, nasal congestion, nasal drainage, rhinorrhea, nasal stinging, sneezing, and change in smell. In accordance to this, patients' overall satisfaction with treatment was mostly rated (around 75%) as satisfied and very satisfied.

On the other hand, facial pain and congestion did not show a significant improvement, as they were rarely present even at day 1. Similarly, nasal dryness was absent in the majority of patients at day 1.

To corroborate subjective data, objective evaluation of progress during treatment was performed through endoscopic evaluation of edema of middle turbinate and nasal secretions. The comparison between endoscopic assessments before and after treatment confirmed edema improvement of the condition in at least 75% of patients.

Moreover, the mean compliance with device administration was 98.47%, showing that adherence to treatment is extremely high. This is a strongly positive feature as it has been demonstrated that poor adherence to topical therapy in CRS patients correlates with worsen symptoms control and higher chance of relapse.²⁶ The paucity and the overall mild features of AEs together with the absence of local negative symptoms (eg, nasal burning or irritation) support the safety of this regimen of nasal washes with Rhinoial™. Both patients and investigators positively evaluated the overall device performance in the study.

Present authors conclude that the usage of nebulized HA nasal hypertonic solution in the form of Rhinoial™ is effective and safe in the treatment of symptoms of CRS. Further study is needed to evaluate efficacy and safety over longer periods in patients with CRS.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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