



An update regarding the treatment of nonallergic rhinitis

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Purpose of review

The review presents some information on known options for treatment of nonallergic rhinitis (NAR) with introduction to new therapies. The merits and limitations of recent advancements in pharmacotherapy of this common problem are briefly discussed as well.

Recent findings

Intranasal corticosteroids are first-line therapy for NAR. Fluticasone propionate and beclomethasone remain the only topical corticosteroids approved for NAR. The use of azelastine – another first-line option – has also been found to be effective even though NAR is a nonallergic entity by definition. Combination of fluticasone propionate and azelastine is a promising option in achieving better symptom reduction. Coadministration of intranasal corticosteroid and topical decongestants is an attractive topic that requires additional safety studies before recommending treatment. Although promising, no scientifically valid recommendation can be made for treatment of NAR with capsaicin. Surgical options in patients with refractory NAR are limited. New studies demonstrate a lack of correlation between objective outcome of radiofrequency ablation of the inferior turbinate and subjective patient symptoms.

Summary

The heterogeneity in clinical presentation makes NAR treatment a daily challenge for otolaryngologists. The diversity of clinical studies with use of unique outcome measures limit systematic reviews which may be instrumental in providing strong recommendations.

Keywords

allergic rhinitis, chronic rhinosinusitis, nonallergic, vasomotor rhinitis

INTRODUCTION

Rhinitis is a nonspecific terminology that is often used to describe patients who present with one or more of the following symptoms: nasal obstruction, rhinorrhea, postnasal drip, pruritis, and sneezing [1]. Rhinitis is classified into allergic and nonallergic subtypes. By definition, the diagnosis of nonallergic rhinitis (NAR) is confirmed by objective exclusion of allergic and infectious disease. The patient with NAR must have an absence of clinically significant immunoglobulin E response to aeroallergens. Although incidence is not well reported, the prevalence of NAR in industrialized countries has been estimated to be 30–40%, thus highlighting the economic burden of treatment and importance of tailoring medical therapy based on proven options [2]. Potential association with chronic sinus disease also heightens the need for employing effective medical treatment strategies as primary modality of therapy or adjuncts to surgical intervention.

The treatment of many diseases is predicated on their pathophysiology; however, the specific pathophysiology involved in NAR is unclear. Neurogenic pathways with postulated parasympathetic hyperactivity from autonomic imbalance have been proposed but remain to be conclusively verified [3,4]. The lack of detailed knowledge of the mechanism of NAR has resulted in classification into eight subtypes based on suspected, clinically determined etiologies [5]. These include idiopathic NAR (formerly known as vasomotor rhinitis), NAR with

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Curr Opin Otolaryngol Head Neck Surg 2016, 24:10–14

DOI:10.1097/MOO.0000000000000225

KEY POINTS

- The spectrum of NAR clinical presentation precludes the selection of a standard regimen for treatment. There is a need for consistency in reported outcome measures in NAR studies to allow for direct comparison and stronger recommendations.
- Combination of nasal corticosteroid and nasal antihistamine sprays has been shown to be more effective than monotherapy from either class.
- Efficacy and safety of capsaicin remains to be substantiated by robust studies.

eosinophilia, atrophic rhinitis, senile rhinitis, hormonal rhinitis or rhinitis of pregnancy, drug induced rhinitis or rhinitis medicamentosa, gustatory rhinitis, and cerebrospinal fluid leak. NAR suspected as cerebrospinal fluid leak deserves another review and is not addressed in this study. As listed above, the phenotypes presented by these classes of NAR occupy a spectrum that can render treatment a challenge. The purpose of this update is to present new information on treatment of NAR and role in treatment of comorbid sinus disease.

INTRANASAL CORTICOSTEROIDS

Nasal corticosteroids have been shown to be effective in the medical management of allergic rhinitis and CRS but with a less defined role in NAR. Fluticasone propionate (available commercially as generic fluticasone, Boehringer Ingelheim/Roxane Laboratories, Columbus, Ohio, USA) and beclomethasone dipropionate (Teva Pharmaceutical Industries, Petach Tikva, Israel) are the only topical nasal corticosteroids approved by the Food and Drug Administration for treatment of NAR. Triamcinolone, flunisolide, and mometasone have also been studied and shown to offer some symptom benefit as well [6–9]. There is no clear evidence favoring a specific nasal steroid spray in NAR at this time and use should be guided by clinical judgment. Of note, patients with weather/temperature sensitive NAR may be poor responders to intranasal corticosteroids thus necessitating early consideration of other pharmacotherapy [10].

COMBINATION OF INTRANASAL CORTICOSTEROIDS AND ANTIHISTAMINES

The heterogeneity in etiology and clinical presentation of chronic rhinitis suggests that combination

therapies may offer patients a greater chance at effective treatment. Combination therapy of fluticasone propionate and azelastine hydrochloride (AZE) – first-line therapies in seasonal allergic rhinitis – has been shown to be more effective compared against monotherapy with either class or placebo in seasonal allergic rhinitis. This combination is otherwise known as MP29–02 (Dymista, Meda Pharmaceuticals, Somerset, New Jersey, USA). This was demonstrated in large randomized double-blind studies with placebo and active controls [11–15]. In addition to treatment of allergic rhinitis, AZE is also approved for treatment of NAR even with unclear mechanism(s) of action in since this is a nonimmunoglobulin E pathophysiology [16].

Recent studies from a collaborative group of authors have investigated the MP29–02 in allergic rhinitis and NAR. Price *et al.* [17] randomized 612 patients with allergic rhinitis or NAR to either receive one spray of MP29–02 in each nostril twice daily (total daily dose of 548 µg AZE and 200 µg fluticasone propionate) or two sprays of fluticasone propionate per nostril in the morning. Patients reported symptoms in an evening reflective total nasal symptom score (rTNSS) diary. The TNSS is a sum of individual symptoms of nasal congestion, pruritis, rhinorrhea, and sneezing that has been used in prior studies investigating azelastine and has recommended by the Food and Drug Administration and European Medicines Agency. More subjects in the MP29–02 group experienced 100% evening rTNSS reduction and did so 9 days faster than the fluticasone propionate group. This, in addition to other outcome measures, led the authors to conclude that MP29–02 is more effective than fluticasone propionate monotherapy in chronic rhinitis with efficacy of MP29–02 extending through the 52-week duration of the study. Long-term safety of this cohort of patients was presented in a subsequent manuscript [18**].

INTRANASAL CORTICOSTEROIDS AND DECONGESTANTS

Nasal decongestants can play a role in NAR treatment by facilitating better distribution of proven nasal corticosteroids and antihistamines. Long-term use of topical decongestants for NAR is typically not encouraged because of systemic side-effects and risk of rebound edema. Although data about safety are limited, coadministration of fluticasone has been found to mitigate the rebound edema when coadministered in patients with allergic rhinitis when used for 2–4 weeks [19,20]. In addition, the combination of mometasone and oxymetazoline over 20 days in patients with allergic rhinitis and NAR

was also found to improve patients' quality of life and objective nasal congestion versus results from placebo and mometasone combination [21]. The premise of better distribution of intranasal corticosteroids with concomitant use of nasal decongestants is an attractive option and begs for additional studies.

INTRANASAL CAPSAICIN

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the active ingredient in chilli peppers. It is a selective agonist of TRP vanilloid 1 ion channel and decreases conduction of nociceptive C-fibers in the trigeminal nerve [22[¶]]. It has been used topically in the treatment of psoriasis, neuralgias, and multiple randomized studies have reported overall therapeutic benefit in idiopathic NAR. Actual mechanism of action in NAR is unknown, but it has been hypothesized that capsaicin may lead to degeneration of these nerve fibers which are involved in local and central neurogenic mechanisms in nasal mucosa. A recent attempt at meta-analysis of four well cited but small randomized controlled studies involving intervention with capsaicin was not possible because of lack of similarity between studies [23[¶]]. In addition, the high bias, methodology issues, diverse primary outcomes, and low quality precluded the presentation of strong recommendations for use of the capsaicin. However, there was a trend that it reduces overall symptoms of NAR when compared with placebo or budesonide.

One recent study by Bernstein *et al.* [24], excluded from the aforementioned review, studied the outcome of a homeopathic preparation of *Capsicum annuum* and eucalyptol. This treatment, also known as ICX72, was compared with placebo (filtered water) in a mixed population of subjects with NAR and/or allergic rhinitis. Eucalyptol was added as an ingredient in treatment to mitigate the burning sensation often reported in past intranasal capsaicin studies. The treated arm involved the use of 1–2 puffs of ICX72 twice daily over 2 weeks. Results showed improvement in TNSS, nasal pain, headache, and sinus pressure compared with placebo with a self-reported quick onset of action (less than a minute). This is the only randomized study to show that scheduled capsaicin may be a well tolerated treatment for NAR. However, the concentration of capsaicin in each actuation of the spray was not reported and the results are confounded by potential cointervention effect of eucalyptol. Currently, no scientifically valid formal recommendation can be made for treatment of NAR with capsaicin.

ANTICHOLINERGICS

Ipratropium bromide (0.03%) is the only topical anticholinergic approved in the treatment of NAR. It is an attractive option when rhinorrhea is a primary symptom as in the case of idiopathic gustatory rhinitis. It has been demonstrated to be well tolerated with no evidence of systemic adverse events with infrequent dryness and epistaxis reported as local side-effects [25,26]. There are no recent studies suggesting a new intranasal anticholinergic or serious adverse events in the use of ipratropium bromide as monotherapy in NAR. Of note, there is no pure oral anticholinergic approved for treatment of NAR. Prior preparations had questionable safety profiles. In addition, side-effects of urinary retention, dry mouth/mucosa, and sedation will likely limit future considerations of oral anticholinergics. Some first generation oral antihistamines such as chlorpheniramine may have anticholinergic activity and have a role in NAR treatment. However, these medications have not been studied specifically in NAR, thus their clinical utility is unknown in these patients.

NASAL SALINE LAVAGE

The role of nasal saline in NAR is undefined. There is no consensus on indication, frequency, and method of delivery of nasal saline in treatment of sinonasal symptoms. It has been studied more in CRS and allergic rhinitis with mixed results. A 2007 Cochrane database review noted that nasal saline alone has not been demonstrated to be beneficial in CRS or more effective than an intranasal corticosteroid [27].

NONPHARMACOLOGIC TREATMENT

Nonpharmacologic options in allergic rhinitis and NAR patients are considered in patients refractory to medical therapy. The reduction of inferior turbinate hypertrophy in patients with predominant symptoms of nasal obstruction is an intuitive intervention. Multiple techniques of inferior turbinate reduction have been shown to be effective. The body of literature for radiofrequency ablation (RFA) continues to grow. RFA of hypertrophied inferior turbinate has been shown to be effective in reducing patient symptoms without causing collateral damage or persistent disruption of ciliary function [28]. However, criteria for selecting patients with NAR that will benefit most from RFA are unclear. Sahin-Yilmaz *et al.* [29[¶]] recently presented a small prospective study noting that the objective outcomes do not correlate with subjective symptomatology in patients who underwent inferior turbinate

RFA. Furthermore, postdecongestion rhinomanometry was also found to predict objective improvement but did not provide information on patients' long-term subjective satisfaction. The lack of correlation between objective outcomes and subjective report should be discussed with patients considering inferior turbinate reduction as part of NAR management.

Kinetic oscillation stimulation (KOS) is a novel experimental approach which has been studied in one center as a nonpharmacologic option for NAR. Juto and Axelsson [30] have suggested that low frequency, low amplitude vibrations from KOS simulate normal nasal mucosa milieu and reduce inflammatory response of the nasal mucosa. Their clinical study reported reduced symptom scores of up to 2 weeks. There is a need for additional basic science and clinical studies to elucidate KOS mechanism of action, safety, and persistence. At this time, it appears to be purely experimental.

In patients with intractable chronic rhinitis, vidian neurectomy may be considered. Although not commonly performed, endoscopic vidian neurectomy has been found to be well tolerated, effective, and associated with less morbidity compared with open vidian neurectomy [31,32].

CONCLUSION

Treatment of NAR is symptom driven because of unclear mechanism of action. Combination therapy of intranasal corticosteroids and antihistamine has emerged as a promising pharmacotherapy for NAR. Studies investigating potential new medications should be completed with use of consistent outcome measures to facilitate comparison between similar studies and allow for combination into larger studies.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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