ARRINEX, INC.

RHINITIS WHITE PAPER

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Rhinitis Whitepaper

A Brief look at Chronic Rhinitis and proposing a novel device base therapy for Patients with Vasomotor Rhinitis

Introduction

Rhinitis is defined as inflammation of the membranes lining the nose, characterized by nasal symptoms, including itching, rhinorrhea, and/or nasal congestion. Chronic nasal symptoms without allergic causation are a broad classification of nasal diseases known as nonallergic rhinitis. As many as half of the patients presenting with nasal symptoms may have this disorder. Nasal symptoms characteristic of nonallergic rhinitis are often indistinguishable from those that occur in allergic rhinitis. Chronic Rhinitis affects tens of millions of people in the US and is a leading cause for patients to seek medical care. Medical treatment has been shown to be effective for allergy suffers but requires daily medication use or onerous allergy treatments and up to 20% of patients may be refractory. For non-allergic rhinitis, few treatments have been shown to be effective for long-term use. A large unmet need exists for a simple, minimally invasive surgical treatment for chronic rhinitis.

Epidemiology and Pathophysiology.

Allergic rhinitis:

Allergic rhinitis (AR) is estimated to affect 35.9 to 79.5 million people in the United States alone. Under normal conditions, the nasal mucosa quite efficiently humidifies and cleans inspired air. This is the result of orchestrated interactions of local and humoral mediators of host defense. In AR, these mechanisms go awry and contribute to the signs and symptoms of the disorder.

The allergic sensitization that characterizes AR has a strong genetic component. The tendency to develop IgE/mast cell/TH2 lymphocyte immune responses is inherited by atopic patients. Exposure to threshold con-centrations of dust mite fecal proteins; cockroach allergen; cat, dog, and other danders; pollen grains; or other allergens for prolonged periods of time leads to the presentation of the allergen by antigen presenting cells to CD4+ T lymphocytes, which then release interleukin (IL)-3, IL-4, IL-5, and other TH2 cytokines. These cytokines drive proinflammatory processes, such as IgE production, against these allergens through the mucosal infiltration and actions of plasma cells, mast cells, and eosinophils.

Once the patient has become sensitized to allergens, subsequent exposures trigger a cascade of events that result in the symptoms of AR. Skin testing can be helpful in determining sensitivity to allergens though positive testing may not indicate the causal agent of the patient's symptoms.

Nonallergic rhinitis:
Non-allergic rhinitis may affect an additional 17 million people. Several studies have helped to establish the frequency of occurrence of allergic versus nonallergic rhinitis as seen in the allergist's office (Table). Mullarkey et al found that 52% of 142 rhinitis patients seen in an allergy clinic could be classified as having nonallergic rhinitis. Enberg evaluated 152 consecutive adults with nasal symptoms and found a 30% frequency of perennial nonallergic rhinitis.

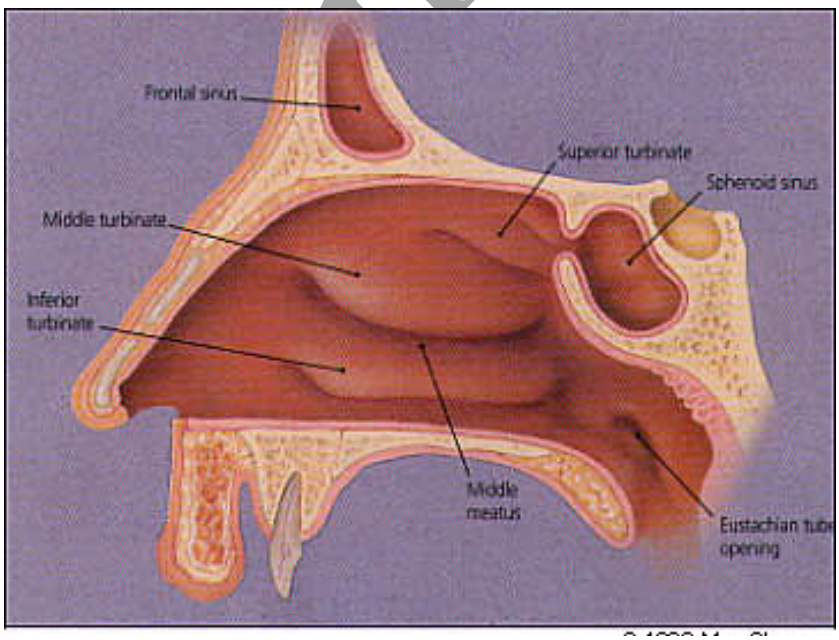
Table 4. Frequency of Occurrence: Allergic vs Nonallergic Rhinitis

Investigator (year)	N	Rhinitis Type		
		Allergic	Mixed	Nonallergic
Mullarkey '80	142	48%	Not studied	52%
Enberg '89	152 (128)*	54%	16%† Undetermined	30%
Togias '90	362	83%	Not studied	17%
ECRHS '99‡	1,412	75%	Not studied	25%

* Diagnosis determined in only 128.
† "Mixed" counted by allergic for total analysis except Enberg's "undetermined group."
‡ European Community Respiratory Health Survey.

Vasomotor rhinitis (VMR) is a major cause of rhinitis unrelated to allergy, infection, structural lesions, systemic disease, or drug abuse. It is a diagnosis of exclusion (eg, negative allergen testing) and is likely to result from many different etiologies. VMR is considered an idiopathic, perennial nonallergic rhinitis associated with negative allergy skin tests to relevant allergens, normal serum IgE levels, and a lack of identifiable inflammation on nasal cytology.

Anatomy



Current Treatments

Medications
Nasal steroids (Flonase, Nasonex, …) and oral anti-histamines (Claritin, Allegra, Zyrtec, …) are the mainstays of medical treatment, but they require daily use and are much less effective against non-allergic rhinitis. Up to 20% of patients are thought to be refractory to non-surgical treatment. Sedating anti-histamines such as Benadryl are used intermittently but the somnolent side effects are not usually well tolerated. Oral steroids can be effective in the short term but carry more severe long term side effects including immunosuppression, Osteoporosis, Cushing syndrome and Diabetes. Adrenergic agents such as Afrin are quite effective for both allergic and nonallergic rhinitis but quickly result in tolerance and "rebound" (recurrence and sometimes worsening of symptoms off the medication).

Nasal Sprays
- Steroids (Flonase, Nasonex, Omnaris)
- Antihistamines (Astelin, Patanase)
- Anticholinergic (Atrovent)
- Adrenergic (Afrin, neosynephrine)
- Saline (Ocean Mist, SinusRinse)

Oral
- Anti-histamines
    - Sedating (Benadryl, Atarax)
    - Non-Sedating (Claritin, Zyrtec, Allegra)
- Steroids (Prednisone, Medrol, Prednisolone)

Surgery
Turbinate reduction surgery (RF and micro-debridement) both have temporary duration of effect of 1-2 years and can result in complications including mucosal sloughing, acute pain and swelling, overtreatment and bone damage. Additionally, turbinate reduction does not treat the symptom of rhinorrhea in allergic and nonallergic rhinitis. The turbinates are autonomically innervated by nerves arising from the Vidian nerve which contains sympathetic and parasympathetic afferents that can modulate the function of the turbinates to either increase (parasympathetic) or decrease (sympathetic) activity of the submucosal layer. It is thought that parasympathetic effect of the vidian nerve predominates so that, on transecting it, the result is decreased rhinitis and congestion. This pathophysiology has been confirmed as surgical treatment of the vidian nerve has been tried with great success; however, the procedure is complicated, time consuming and potentially can result in dry eyes due to autonomic fibers in the vidian nerve that supply the lacrimal glands.

Immunotherapy (allergy shots)

Immunotherapy for allergic disease involves the gradual administration of increasing amounts of allergen to which the patient is sensitive, for the purpose of modulating the untoward immune response to that allergen and alleviating allergic symptoms. Immunotherapy is currently the only treatment that alters the abnormal immune response underlying allergic disease. Subcutaneous injection immunotherapy (SCIT) is the established form of this treatment. Oral forms of immunotherapy are under research and limited use among early adopters. Oral therapy may have the advantage of convenience and lower anaphylactic risk of the comparative efficacy is unclear. Dermal immunotherapy is currently under development as well. Typically, immunotherapy is used when patients have unsatisfactory control with pharmacotherapy as discussed above. Insurance coverage for SCIT is poor resulting in thousands of dollars in out of pocket cost to the patient. The efficacy of SCIT appears somewhat comparable to nasal steroid treatment for allergic rhinitis during the maintenance treatment period of three to five years which is quite long duration for most patients to tolerate. Studies showed the relapse rate 62 percent after less than three years of treatment and 48 percent after more than three years.

Conclusion

Allergic and nonallergic rhinitis impact tens of millions of patients frequently with severe distressing symptoms. Current standard therapy require daily nasal steroid and oral anti-histamine use for symptom control but up to 20% of patients are refractory to medical treatment. Additionally, nasal steroids and oral anti-histamines are not very effective against nonallergic rhinitis. Allergy shots require more than three years of regular injections, are no more effective than nasal steroids, and are costly and inconvenient with a high relapse rate. Surgical treatment with turbinate reduction does not significantly improve symptoms other than congestion. Vidian neurectomy is an complex procedure that is highly effective but can result in dry eye. A large unmet need exists for a minimally invasive long lasting treatment for rhinitis conveniently administered in a single treatment.