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Sublingual Immunotherapy for Allergic Fungal Sinusitis

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Abstract

Allergic fungal sinusitis (AFS) is a condition that has an allergic basis caused by exposure to fungi in the sinonasal tract leading to chronic inflammation. Despite standard treatment modalities, which typically include surgery and medical management of allergies, patients still have a high rate of recurrence. Subcutaneous immunotherapy (SCIT) has been used as adjuvant treatment for AFS. Evidence exists to support the use of sublingual immunotherapy (SLIT) as a safe and efficacious method of treating allergies, but no studies have assessed the utility of SLIT in the management of allergic fungal sinusitis. A record review of cases of AFS that are currently or previously treated with sublingual immunotherapy from 2007 to 2011 was performed. Parameters of interest included serum IgE levels, changes in symptoms, Lund-McKay scores, decreased sensitization to fungal allergens associated with AFS, and serum IgE levels. Ten patients with diagnosed AFS were treated with SLIT. No adverse effects related to the use of SLIT therapy were identified. Decreases in subjective complaints, exam findings, Lund-McKay scores, and serum IgE levels were observed. Thus, sublingual immunotherapy appears to be a safe adjunct to the management of AFS that may improve patient outcomes.

Keywords

sublingual, immunotherapy, fungal, sinusitis, allergic, AFS, rhinosinusitis, SLIT, allergy, SCIT

Introduction

Allergic fungal sinusitis (AFS) continues to be a common cause of chronic nasal obstruction and an indication for endoscopic sinus surgery. Allergic fungal sinusitis is a noninvasive, noninfectious form of sinusitis mediated by an allergic and immunologic response to common, ubiquitous fungi that are present within the paranasal sinuses.[1-3] The result of this response is chronic allergic hypertrophic rhinosinusitis.[1] While in some forms of fungal sinusitis fungal organisms invade the tissue (acute necrotizing, chronic invasive, granulomatous invasive), AFS is distinguished by having no histologic invasion by the fungi.[1,2]

The current management of AFS includes surgery, maintenance of adequate sinus drainage, and allergy medical therapy.[3,4] Endoscopic sinus surgery is usually indicated to remove hypertrophic mucosa, fungal elements, and thick allergic mucin.[1] Following surgery for AFS, treatment will typically include sinus irrigation with saline, systemic antihistamines, and intranasal or systemic corticosteroids.[1,3] Although it may seem counterintuitive, topical or systemic antifungal therapy has not been shown to be beneficial.[1-4] Systemic corticosteroids have been shown to provide substantial benefit when used postoperatively.[1-3]

Increasingly, allergy immunotherapy (AIT) has become an important therapeutic adjunct to the treatment of AFS.[5,6] Specific allergen immunotherapy directed toward causative fungal species provides an attractive treatment strategy for AFS based on our current understanding of its pathophysiology. While no randomized, placebo-controlled studies have demonstrated benefit for immunotherapy in the management of AFS, uncontrolled studies do support its use.[2-9]

Specific allergy immunotherapy in the United States is given primarily by the subcutaneous route. While numerous studies have shown subcutaneous immunotherapy (SCIT) to be safe and suggested efficacy, its widespread use is limited by the inconvenience of weekly office visits for patients to receive injections and rare cases of anaphylaxis. One recent clinical study by Greenhaw et al[10] showed no difference in adverse reactions between the group with AFS receiving

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Table 1. Bent and Kuhn[17] Major Diagnostic Criteria.

Type I hypersensitivity reaction to associated fungi
Clinical evidence of nasal polyposis
Characteristic radiographic appearance on computed tomography
Positive fungal stains on pathology
Eosinophilic mucin without tissue invasion by fungal elements

subcutaneous immunotherapy and a control group in patients without AFS. Both groups received standardized doses of SCIT and showed no difference in immediate or delayed local reactions, dose adjustments, or administration complications. There were no systemic complications reported in the study, which suggests that it is safe to undergo immunotherapy with AFS without an increased complication rate. Increasingly, sublingual immunotherapy (SLIT) is being recognized as an effective and convenient method of providing allergy immunotherapy. Many well-designed studies and at least 2 systematic reviews support the use of SLIT for management of allergy patients.[9,11] While previous studies of immunotherapy for AFS have focused on the use of SCIT, no studies have assessed the benefit of SLIT in the management of AFS.

Methods and Materials

Using our institution's electronic medical record, we searched for patients with the diagnosis of allergic fungal sinusitis. All patients included in this review were diagnosed as having AFS based on established criteria (Table 1).

The records were then reviewed for clinical course, results of modified radioallergosorbent system testing (MRAST), and SLIT administration. The MRAST is an in vitro enzyme immunoassay used to measure allergen specific responses. Additionally, sinus computed tomography (CT) scans were reviewed by a single unblinded provider and specifically assessed for the extent of sinus involvement using Lund-McKay scores.[12] Where available, posttreatment sinus CTs were evaluated for changes in Lund-McKay scores.

All patients received SLIT antigen mix provided by the Otolaryngology Department at Naval Medical Center Portsmouth, which was procured from Allergychoices Pharmacy (Onalaska, Wisconsin, USA). Antigens were combined in a 15 ml bottle that contained glycerin as the diluent. Antigen formulation was based on the La Cross Protocol using MRAST test results.[13] As specified in this protocol, antigen was initiated at 1 dilution level below the MRAST result. For example, a patient with a class 2 reaction to *Aspergillus fumigatus* would be started at dilution 3. The initial reactions were based on allergen-specific IgE levels and divided into classes based on severity. Multiple antigens were included in the vials per the MRAST results (both inhalant and mold). Individualized SLIT antigen mix records were kept on file in the allergy clinic of the otolaryngology service at Naval Medical Center Portsmouth. Patients then underwent dose escalation of inhalant allergens every 3 months and mold allergens every 6 months. All portions of this study were in compliance with Institutional Review Board protocol number NMCP.2011.0015 at Naval Medical Center Portsmouth.

Results

Our review identified 10 patients diagnosed with AFS whose treatment included SLIT. Individual patient characteristics are contained in Table 2. The average patient age was 32 years. All patients underwent functional endoscopic surgery prior to administration of SLIT with the exception of 1 patient. Of the 10 patients identified in this review, 2 were lost to follow-up. A review of the clinical complaints and office examination findings for the remaining 8 patients demonstrated consistent improvement in sinonasal symptoms and examination findings. No adverse reactions to SLIT were identified.

Of the 8 remaining patients not lost to follow-up, the duration of SLIT treatment ranged from 13 to 43 months (average 28 months), 6 had postoperative CT scans ranging from 3 to 18 months (average 11 months), and 7 had pre- and posttreatment MRAST testing at intervals between 13 to 50 months (average 26 months). Review of the 6 patients with postoperative CT scans showed changes in Lund-McKay scores ranging from −13 to +2 (average −4), with clear improvement in 4 of 6 patients by scores of −13 to −2. Of these 6 patients, 2 required reoperation: 1 patient that worsened by 2 points and 1 that improved by 10 points. The latter patient was the only patient that started SLIT prior to undergoing endoscopy sinus surgery. Reoperation was performed 7 months after the original surgery.

Records were also reviewed for results of in vitro allergy testing (MRAST), which included specific testing for 6 common fungi (Table 3). The most common fungal allergens encountered were *Alternaria tenuis* (10 of 10 patients), *Curvularia lunata*, and *Aspergillus fumigatus* (7 of 10 patients each). Patients affected by *Alternaria tenuis* allergy tended to have the higher MRAST allergy classes. MRAST scores improved with SLIT in 6 patients for most fungal allergens. However, increased duration of treatment did not correlate with improvement in MRAST results. Total serum IgE measurement improved in all patients except 1. This patient did not require reoperation. Interestingly, the 2 patients that required reoperation had seropositivity to all 6 of the common fungal allergens in Table 2. Furthermore, both patients had required multiple revision surgeries, and 1 of the patients began SLIT prior to surgery, which is associated with treatment failure.

Discussion

The cornerstone of AFS treatment has included surgical extirpation of the allergic mucin and polyps with maintenance of

Table 2. Clinical Course of Patients Treated for Allergic Fungal Sinusitis.[a]

Patient	Age	Duration of SLIT (mo)	Time Between Pre/Postoperative CT (mo)	Change in Lund-McKay Score	Clinical Improvement	Repeat Surgery
1	22	27	3	−13	No polyps noted 27 months postoperatively. Symptoms controlled with medications.	No
2[b]	43	7	NA	NA	No polyps noted 7 months postoperatively.	No
3	29	13	NA	NA	No nasal congestion, hyposmia, sinus pressure, or polyp regrowth 12 months postoperatively	No
4[b]	29	2	NA	NA	No epistaxis or nasal pain, minimal polyp disease 2 months postoperatively	No
5	55	27	9	+2	Increased interval between surgeries from 9 months to 13 months on SLIT	Yes (Oct 2011)
6	21	29	13	−10	Marked improvement in nasal airflow with medications. Increased interval between surgeries from 7 to 11 months while on SLIT. No polyp regrowth 9 months after last procedure.	Yes (May 2011)
7	19	28	18	−12	No polyp regrowth at 2 months postoperatively	No
8	35	31	NA	NA	Increased nasal airflow, no hyposmia, symptoms controlled with medications. No polyps 15 months postoperatively on FFL.	No
9	29	43	16	+1	Improved airflow and no hyposmia. Minimal polypoid disease (nonprogressive) 38 months postoperatively	No
10	40	26	9	0	Reduced congestion, minimal polypoid disease with no AFS at 15 months postoperatively	No

[a]NA indicates no data available. AFS, allergic fungal sinusitis; CT, computed tomography; FFL, flexible fiberoptic laryngoscopy; SLIT, sublingual immunotherapy.
[b]Lost to follow-up.

adequate sinus drainage followed by medical therapy. Medical treatment typically consists of some combination of topical intranasal steroids, antihistamines, nasal irrigations, office debridements, and systemic corticosteroids. Previous uncontrolled studies have demonstrated benefit to SCIT.[2-7] Likewise, the safety of SCIT has been established when initiated after surgical debulking. In the United States, SLIT is rapidly gaining acceptance for the treatment of inhalant allergy. While the safety and efficacy of SLIT for allergy treatment has been well studied, no published studies have assessed the safety and efficacy of SLIT for the treatment of AFS.[14,15] Therefore, we sought to evaluate the safety and efficacy of SLIT in this series of 10 AFS patients.

AFS is a noninvasive fungal rhinosinusitis characterized as an inflammatory, hypersensitivity disorder rather than a true fungal infection.[2] Dematiaceous (darkly pigmented) fungal elements found in the environment are thought to trigger an immune response. These include *Bipolaris spicifera, Curvularia, Exserohilum*, and *Alternaria* species. After Dematiaceous fungi, *Aspergillus* species are the next most common.[1-3] Once the inflammatory cascade is activated, inflammatory mediators slowly damage nasal mucosa.[3] Nasal polyps and proinflammatory eosinophilic-rich allergic mucin fill the sinuses unilaterally or sometimes bilaterally, often expanding the opacified sinus. High titers of fungal specific IgE are found, and total serum IgE can be elevated.[2]

The typical AFS patient is an immunocompetent, young person with a history of atopic disease.[1-3] The usual presentation will include nasal dyspnea, rhinorrhea, and nasal polyps.[16] Signs and symptoms of this disease may resemble infectious sinusitis because of complaints of sinus pressure, purulent drainage, and pain. AFS patients may specifically report black-brown rubbery material discharged from the nose.[1] The histopathologic hallmark of AFS is thick allergic mucin that is comprised of mucus, masses of eosinophils, and Charcot-Leyden crystals.[1-3] This thick allergic mucin may obstruct sinus drainage and is very difficult for patients to expel from the sinonasal tract.

The diagnosis of AFS is based on the use of well-established criteria that include 5 elements: evidence of Gell and Coombs type I hypersensitivity (IgE mediated), nasal polyposis, characteristic CT findings, eosinophilic mucin, and positive fungal smear.[17] Associated criteria include asthma, unilateral predominance, radiographic bone erosion, fungal culture, Charcot-Leyden crystals, and serum eosinophilia.[17] In establishing the diagnosis of AFS, it is important

Table 3. Comparing Fungal Allergen MRAST Classes Pre- and Posttreatment With Testing Interval Included.[a]

Patient	Interval Between Assessment (mo)	*Aspergillus fumigatus*		*Mucor racemosus*		*Alternaria tenuis*		*Rhizopus nigricans*		*Curvularia lunata*		*Aspergillus niger*		Serum IgE (IU/ml)	
MRAST		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	21	3	2	1	1	5	4	0	—	2	0	1	0	521	137
2[b]	—	0	—	0	—	4	—	0	—	0	—	0	—	144	—
3	13	1	0	0	—	5	4	0	1	2	2	0	0	327	165
4[b]	—	1	—	0	—	4	—	0	—	2	—	0	—	278	—
5	27	3	2	2	1	4	1	2	2	3	2	3	2	1072	2995
6	24	2	2	2	1	3	1	2	1	3	2	1	1	1761	359
7	16	2	1	—	2	4	4	—	3	3	3	—	2	—	3872
8	29	0	—	0	—	3	4	0	—	0	2	0	0	52	33
9	50	2	1	3	2	4	4	1	1	4	4	1	1	1323	492
10	18	0	0	0	0	5	4	0	1	0	2	0	0	233	301

[a]— indicates value not available. MRAST, modified radioallergosorbent system testing; post, posttreatment; pre, pretreatment.
[b]Lost to follow-up.

that other forms of fungal sinusitis are excluded.[1] Mabry et al[9] reported excellent clinical response in the treatment of AFS with SCIT following appropriate surgical extirpation. Furthermore, they demonstrated safety and efficacy in some limited studies and observed that there were no adverse consequences from introducing additional fungal antigen. Ferguson[18] reviewed 7 patients who received SCIT, 5 of whom failed to improve or worsened. However, it is important to note that this group received immunotherapy prior to sinus surgery.[18] Two patients in this study who received SCIT after sinus surgery responded well. In another study, Mabry and Mabry[8] compared 2 groups of AFS patients treated with the identical regimen except that 1 group received SCIT. The results demonstrated a statistically significant improvement in quality of life scores and endoscopic mucosal staging in the immunotherapy group. Furthermore, all control group patients required an average of 2 courses of systemic corticosteroids, whereas the immunotherapy group required none.[1,6] The protocol for immunotherapy, thus proposed by Mabry and Mabry,[6] is to perform in vitro allergy testing (MRAST) and/or skin testing either before or after surgery.[2-9] Following surgery, immunotherapy is started within 4 to 6 weeks.[2-6] All positive mold reactions are included in the customized antigen mixture used for the immunotherapy.[5,6,8] The authors recommend treatment of all molds that test positive rather than simply treating for the mold species cultured from the sinuses.[5-8]

SLIT has been utilized extensively in Europe for over 2 decades to safely and effectively treat inhalant allergy. In recent years, the advantages of SLIT have been increasingly recognized in the United States. Due to the ease and convenience of self-administration and an outstanding safety profile, patient compliance is enhanced and is presumed to translate into improved outcomes. At Naval Medical Center Portsmouth, we currently have over 300 patients receiving SLIT to treat their inhalant allergies. Our active duty military population with a high operational demand has benefited from the option to continue immunotherapy even when deployed to foreign soil or underway on ships, circumstances that would typically contraindicate the use of SCIT. In this review, we identified 10 patients treated at our facility for AFS with SLIT. Our review of clinical, laboratory, and radiographic records demonstrated that all 8 of the patients available for follow-up achieved clinical improvement. Our recurrence rate of 20% is lower than the average rate in current literature.[19] The 2 patients in this series that required reoperation were allergic to all 6 of the common fungal allergens, and 1 of these patients was started on SLIT prior to surgery. As noted previously, Ferguson[18] has recognized initiation of immunotherapy prior to surgery as a risk factor for treatment failure. No adverse reactions to SLIT were seen in our series.

The observed clinical improvements seen in our AFS patients are also supported by laboratory and radiographic data. As noted previously, we observed a net reduction in MRAST scores as well as total serum IgE levels for most patients. Total serum IgE levels, while not definitively correlated with clinical improvement, demonstrated substantial decreases between pre- and post-SLIT therapy in the majority of patients, supporting the expected immunologic response to SLIT.[20] Clinical correlation between rhinosinusitis and total serum IgE levels has been shown in some studies, although not necessarily seen in AFS patients.[21] Notably, the patient with the largest posttreatment increase in IgE was one who required revision surgery. Literature discussing the utility of SLIT in the treatment of allergen-based disease has increased during this decade, indicating an interest in the otolaryngology community to study its efficacy. A recent review by Doellman et al[22] provided further evidence that SLIT remains a safe adjunctive treatment and can be used in AFS; however, more substantial

prospective studies have been lacking. The authors did not report any increased incidence of type III-mediated reactions, severe local reactions, or delayed reactions to SLIT.[22] Lund-Mckay scores also decreased for the majority of patients, indicating improved sinonasal drainage in the postoperative period. While this cannot be solely attributed to the addition of immunotherapy and is most likely due to the benefit of surgery, the addition of these data correlated with subjective improvement seen in these patients. Furthermore, CT scans were obtained in some patients long after surgical debridement, lending support to the continued benefit of the medical treatment regimen.

We fully recognize that our case series contains several important limitations. Due to the small sample and retrospective design without a comparison group, we cannot definitively attribute the clinical improvement seen in our patients to adjunctive treatment with SLIT, and the subjective improvements were not quantified using a standardized quality of life scale. Still, our series does lend support for the use of SLIT as a possible addition to the current treatment of AFS with a reduction in clinical symptoms, MRAST scores, and serum IgE as well as a decreased need for further surgery. No adverse events were reported, and administration was much simpler than for subcutaneous immunotherapy. This study therefore serves as a pilot study showing the safety of adding SLIT to a population with AFS and a possible benefit with good clinical results. Prospective studies would be helpful in further supporting this claim before implementing SLIT as part of the standard treatment regimen for allergic fungal sinusitis.

Conclusion

Allergic fungal sinusitis treatment consists of surgical extirpation of the allergic mucin and polyps with maintenance of adequate sinus drainage followed by medical therapy consisting of topical intranasal steroids, antihistamines, nasal irrigations, office debridements, and systemic corticosteroids. Immunotherapy has shown to be of benefit as a treatment adjunct in some studies, and the safety profile of subcutaneous immunotherapy is firmly established. Sublingual immunotherapy offers enhanced ease of treatment and compliance, particularly in the active duty military population, and SLIT appears to be a safe, and possibly effective, addition to the treatment of allergic fungal sinusitis. Subjective and objective patient improvements were seen in the majority of AFS patients while on SLIT postoperatively, and there were no adverse effects reported in any of the patients over a follow-up period of almost 4 years. Additionally, no local reactions or complications were reported by or observed in any of the patients. Future prospective studies should be conducted to further clarify the role of SLIT in the management of AFS.

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Authors' Note

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