

Fungal immunotherapy in patients with allergic fungal sinusitis

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Background: Allergic fungal sinusitis is a disease for which optimal treatment is unclear. Previous studies using fungal immunotherapy reported less recurrence after surgery. There has been concern that traditional high-dose immunotherapy could induce systemic hypersensitivity in patients with this condition.

Objective: To determine the safety of high-dose subcutaneous fungal immunotherapy in patients with allergic fungal sinusitis.

Methods: Safety of high-dose subcutaneous fungal immunotherapy was assessed in 14 patients from our clinic who met diagnostic criteria for allergic fungal sinusitis. Results were compared to a control group of 14 patients with chronic rhinosinusitis without allergic fungal sinusitis who received subcutaneous fungal immunotherapy. We also performed a literature search to identify all previous reports of subcutaneous fungal immunotherapy.

Results: No differences between numbers of immediate local or large local reactions, delayed local reactions, or required dose adjustments were noted between patient and control groups. One patient from each group experienced a mild systemic urticarial reaction to immunotherapy. Similarly, there were no differences in complications in either group that also received immunotherapy with nonfungal allergens. No patient developed evidence of immune complex disease. Eight publications were identified for inclusion in our literature analysis, 7 of which used low-dose subcutaneous immunotherapy. None of these noted complications more serious than local reactions.

Conclusion: Our data demonstrate that subcutaneous fungal immunotherapy in patients with allergic fungal sinusitis is unlikely to cause adverse reactions than those occurring with pollen immunotherapy. Clinical trials of high-dose, traditional immunotherapy with fungal allergens for efficacy may proceed in patients with allergic fungal sinusitis without undue concern.

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INTRODUCTION

Allergic fungal sinusitis is a form of chronic rhinosinusitis characterized by the production of large quantities of eosinophil-rich allergic mucin containing fungal elements within the sinuses.^{1,2} This allergic mucin obstructs normal drainage pathways of the paranasal sinuses and results in chronic bacterial sinusitis. Moreover, accumulations of allergic mucin may expand outside the paranasal sinuses into the orbit and intracranial structures.

The disease appears to result from fungal specific IgE-driven allergic inflammation similar to that seen in allergic bronchopulmonary mycosis.³ Indeed, allergic fungal sinusitis and allergic bronchopulmonary mycosis coexist often enough to have been termed *sinobronchial allergic mycosis*, the sinobronchial allergic mycosis syndrome.⁴ Diagnostic criteria for allergic fungal rhinosinusitis have been previously established.^{5,6}

The natural history and appropriate treatment of allergic fungal sinusitis are unclear. Available data suggest that it is a

chronic disease associated with chronic sinusitis, nasal polypsis, multiple sinus operations, and varying levels of disability.⁷ Some patients develop mucosal damage in the form of atrophic rhinosinusitis.⁸ Treatment has been empiric and usually consists of prolonged corticosteroid therapy that induces significant adverse effects in many patients.⁹⁻¹¹

Allergen immunotherapy has been used for many years to treat IgE-mediated hypersensitivity diseases, including rhinosinusitis and asthma.¹² The treatment efficacy of allergen immunotherapy has been established in control trials in pollen-induced and some fungal-induced (*Alternaria*) allergic rhinosinusitis.¹³ Some attempts to down-regulate allergic inflammation in allergic fungal sinusitis with immunotherapy to fungal allergens have been reported.^{6,14-16} By far the largest experience with fungal immunotherapy for allergic fungal sinusitis has been published by Mabry and colleagues.¹⁷⁻²³ Their work suggests that allergen immunotherapy to fungal allergens may be effective in the treatment of symptoms of allergic fungal sinusitis and decreases the rate of allergic fungal sinusitis exacerbations postoperatively and further operations.

There have been concerns that fungal immunotherapy could cause immune complex disease in patients with allergic bronchopulmonary aspergillosis and allergic fungal sinusitis who have fungal specific IgG and IgE.^{10,24} In this study, we reviewed our experience with subcutaneous immunotherapy to fungal allergens in a group of patients with allergic fungal sinusitis in our clinics. Our particular interest was to establish

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the safety of this approach in the face of what we believe is some evidence of efficacy in controlling a disease for which few other safe and effective therapies are available.

METHODS

Inclusion Criteria for the Study Patients

We reviewed immunotherapy records in our allergy clinic and determined that 16 patients with allergic fungal sinusitis had been given immunotherapy within the last 10 years. Fourteen of these patients (1) met published diagnostic criteria for allergic fungal sinusitis;⁶ (2) had received immunotherapy to fungal allergens for a minimum of 6 months; and (3) had adequate records to determine the outcome variables of interest. Diagnostic criteria for allergic fungal sinusitis include the following: radiographic evidence of sinusitis, the presence of gross or histopathologic eosinophil-rich allergic mucin, a positive fungal stain or culture from the sinuses, absence of fungal invasion of the epithelium, and absence of contributory factors, such as diabetes mellitus or immunodeficiency.⁶

Immunotherapy Protocol

Skin prick (epidermal) testing with 1:20 or 1:40 (wt/vol) 50% glycerinated stock commercial extracts were performed. When skin prick test results were negative, additional intradermal skin tests with 0.02 mL of extract diluted 1:1,000 were performed. Skin test results were scored positive or negative using conventional scoring systems.²⁵ A panel of 52 inhalant allergens was used, including 10 fungal allergens. Those fungal and inhalant allergens inducing 2+ or greater skin prick test results or 2+ or greater intradermal responses were used for immunotherapy. Subcutaneous immunotherapy in our patients was administered using traditional techniques.²⁶ Stock commercial glycerinated allergen extracts (1:10 or 1:20) were diluted 10-fold using 10% glycerin in phenol saline (Greer Laboratories, Lenoir, North Carolina). An extract was formulated using 0.5 mL for each allergen in a total volume of 5 mL. The full-strength extract was a 1:10 dilution of the allergens from the stock extract. Five 10-fold dilutions constituted the immunotherapy regimen. Up to 10 allergens could be included in the full-strength extract from which 10-fold dilutions were made. This provided 5 injection vials with the 1:10 (full-strength) dilution being the desired maximum (maintenance) concentration. Patients proceeded through a defined protocol from the 1:100,000 dilution of the maintenance concentration to a maximum dose of 0.5 mL of the full-strength dilution or to the highest concentration of the extract tolerated (maintenance dose).

Untoward Reactions to Immunotherapy

Records of the 16 patients with allergic fungal sinusitis on allergen immunotherapy were reviewed for evidence of systemic or local cutaneous reactions. These records are routinely kept in our clinic and are used in decision making for the progression from dilute to concentrated allergen immunotherapy. When large local, delayed large local, or systemic

reactions occur, subsequent doses of immunotherapy are reduced. Patients were said to have *systemic allergic reactions* if they had generalized pruritus or urticaria, angioedema, asthma, or frank anaphylaxis occurring within 1 hour of allergen immunotherapy or required treatment with epinephrine for any symptom. Sizes of local cutaneous reactions were documented on all patients and were measured as the greatest diameter of the wheal reaction 30 minutes after the administration of immunotherapy. For the purposes of this study, wheal reactions 15 to 19 mm were termed *local reactions* and reactions 20 mm or greater were termed *large local reactions*. *Late local reactions* were defined as troubling areas of edema and pain at the injection site that were reported by the patients 6 to 24 hours later.

The dose adjustment for large local reactions was the administration of the previous dose that did not cause a local reaction, termed *back titration*.²⁷ Subsequent doses were increased weekly from that point to the highest tolerated dose (maintenance dose), which was given every 3 to 4 weeks thereafter. The dose adjustment for delayed local reactions was a 50% reduction of the volume of the next dose. Systemic reactions were evaluated by a physician who specified the next dose, usually a 10-fold reduction in concentration.

Control Group

Billing records were used to identify patients with chronic rhinosinusitis without allergic fungal sinusitis or allergic bronchopulmonary mycosis who were undergoing immunotherapy to fungal allergens for more than 6 months. The first 14 patients so identified formed the *control group*. Immunotherapy records were similarly reviewed to determine the prevalence of local and systemic reactions to allergen immunotherapy.

Review of the Literature on Allergen Immunotherapy for Allergic Fungal Sinusitis and Allergic Bronchopulmonary Mycosis

Using the MEDLINE and PubMed search engines, we performed separate computer-based searches on (1) immunotherapy AND allergic fungal sinusitis; (2) complications of allergy immunotherapy in allergic fungal sinusitis; (3) bronchopulmonary allergic mycosis AND immunotherapy; and (4) bronchopulmonary allergic mycosis AND allergic fungal sinusitis AND immunotherapy. We used MeSH terms with the following limits: English language only and publication dates from 1988 to 2009. The 1988 starting date reflected the publication of diagnostic criteria for allergic fungal sinusitis.

Criteria for inclusion of our analysis were as follows: (1) patients met published diagnostic criteria for allergic fungal sinusitis;⁶ (2) the article was an original report of results of immunotherapy; and (3) immunotherapy was given only for those fungal allergens to which the patients had positive epicutaneous or intradermal allergy skin test results or positive radioallergosorbent test results to fungal allergens.

Statistical Analysis

Results were reported as mean $\pm$ SD. This study was approved by the Institutional Review Board of the University of Mississippi Medical Center (No. 2008-0106) as a retrospective medical record review not requiring informed consent.

RESULTS

Allergen Immunotherapy With Fungal Allergens for Allergic Fungal Sinusitis

Using the outlined inclusion criteria, we identified 14 patients with allergic fungal sinusitis who received allergen immunotherapy to fungi for 6 months or longer. Two of the 16 patients who received allergen immunotherapy were excluded because of an inadequate duration of treatment. Demographic data on these patients and those in the control group were similar in number, age, race, and sex (Table 1). Patients and controls received immunotherapy regimens that included allergens other than fungal allergens, primarily pollens. It is our custom to administer mold allergens in separate extracts from other allergens. However, only 5 in the allergic fungal sinusitis group and 4 in the control group in this series conformed to that custom, reflecting the referral nature of our practice. The most common fungal allergens administered were *Curvularia*, *Alternaria*, *Aspergillus*, *Epicoccum*, *Penicillium*, and *Helminthosporium* in descending order (Table 2). There were no differences in the number of local reac-

Table 2. Number of Fungal Allergens in Immunotherapy Extracts

Fungus	Allergic fungal sinusitis patients (n = 14)	Controls (n = 14)
<i>Alternaria</i>	11	7
<i>Aspergillus mix</i> ^a	9	5
<i>Bipolaris</i>	6	3
<i>Cladosporium</i>	4	2
<i>Curvularia</i>	12	6
<i>Epicoccum</i>	9	2
<i>Fusarium solani</i>	8	3
<i>Helminthosporium (Drechslera)</i>	8	2
<i>Hormodendrum</i>	1	0
<i>Mucor plumbeus</i>	2	3
<i>Penicillium notatum</i>	8	6
<i>Stemphylium</i>	7	4

^a *Aspergillus mix* used in patients with allergic fungal sinusitis and controls was composed of *Aspergillus fumigatus* and *Aspergillus flavus*.

tions, large local reactions, late local reactions, or back titrations among the patient and control groups (Table 1).

Results of immunotherapy to nonfungal allergens were also evaluated in patient and control groups (Table 3). No differences in the number of local reactions, large local reactions, late local reactions, or back titrations were noted between patients with allergic fungal sinusitis and control groups.

Table 1. Demographic Data and Results of Immunotherapy to Fungal Allergens in Study Patients

Characteristics	Allergic fungal sinusitis patients (n = 14)	Controls (n = 14)
Age, mean $\pm$ SD, y	36.6 $\pm$ 12.8	40.1 $\pm$ 11.9
Sex, No. (%)		
Female	8 (57)	9 (64)
Male	6 (43)	5 (36)
Race, No.		
White	9	9
Black	5	5
Fungi in extract, mean $\pm$ SD	6.0 $\pm$ 2.2	3.1 $\pm$ 2.2
Total time on immunotherapy, mean $\pm$ SD, mo	21.8 $\pm$ 12.9	22.9 $\pm$ 23.7
Total No. of local reactions = 15 mm, mean $\pm$ SD	2.4 $\pm$ 2.7	1.8 $\pm$ 1.9
Total No. of local reactions = 20 mm, mean $\pm$ SD	0.6 $\pm$ 0.8	0.5 $\pm$ 0.9
Total No. of late local reactions, mean $\pm$ SD	1.1 $\pm$ 1.7	0.8 $\pm$ 1.2
No. of local reactions = 15 mm per month, mean $\pm$ SD	0.1 $\pm$ 0.1	0.09 $\pm$ 0.1
No. of immunotherapy back titrations, mean $\pm$ SD	1.6 $\pm$ 1.9	1.3 $\pm$ 1.5
No. of immunotherapy back titrations per month, mean $\pm$ SD	0.07 $\pm$ 0.07	0.08 $\pm$ 0.1

Table 3. Injection Site Reactions to Nonfungal Allergen Immunotherapy in Patient and Control Groups

Reaction	Allergic fungal sinusitis patients ^a (n = 7)	Controls (n = 12)
No. of nonfungal allergens in extract, mean $\pm$ SD	8.4 $\pm$ 5.0	9.6 $\pm$ 5.4
Total time undergoing immunotherapy, mean $\pm$ SD, mo	20 $\pm$ 11.2	-24 $\pm$ 25.2
Total No. of local reactions >15 mm, mean $\pm$ SD	3.4 $\pm$ 3.5	2.6 $\pm$ 3.1
Total No. of local reactions >20 mm, mean $\pm$ SD	0.4 $\pm$ 0.8	1.0 $\pm$ 2.3
Total No. of late local reactions, mean $\pm$ SD	1.3 $\pm$ 2.4	1.5 $\pm$ 2.4
No. of local reactions >15 mm per month, mean $\pm$ SD	0.1 $\pm$ 0.1	0.1 $\pm$ 0.1
No. of immunotherapy back-titrations, mean $\pm$ SD	1.7 $\pm$ 2.6	1.5 $\pm$ 1.5
No. of immunotherapy back titrations per month, mean $\pm$ SD	0.06 $\pm$ 0.08	0.09 $\pm$ 0.11

^a Three patients with allergic fungal sinusitis were receiving extracts of nonfungal allergens from other allergists. Data for these patients were excluded from the table.

One patient with allergic fungal sinusitis reported a systemic reaction to allergen immunotherapy, described as generalized pruritus and a large local reaction. The patient received pollen immunotherapy at a different location from another physician, who was uncomfortable administering fungal immunotherapy to a patient with allergic fungal sinusitis. This reaction is safely attributed to his fungal extract, which contained the following fungal allergens: *Alternaria*, *Aspergillus*, *Helminthosporium*, *Cladosporium*, *Penicillium*, *Curvularia*, and *Fusarium*. After back titration of the fungal extract, the patient continued immunotherapy to a maintenance dose of 0.25 mL of the 1:10 vial without further systemic reactions. One patient from the control group experienced a systemic reaction that consisted of generalized pruritus and wheezing. The following fungal allergens were included in her extract: *Alternaria*, *Aspergillus*, and *Curvularia*. This patient discontinued immunotherapy after the reaction.

The mean number of months of fungal immunotherapy was similar for allergic fungal sinusitis (21.8 ± 12.9) and for the control group (22.9 ± 23.7). No patient developed clinical evidence of nephritis, hypersensitivity vasculitis, other systemic hypersensitivity, or autoimmunity while undergoing immunotherapy or thereafter in follow-up for up to 5 years.

The percentages of allergic fungal sinusitis (57%) and control (57%) patients reaching full-strength doses of fungal immunotherapy were similar. The percentages of allergic fungal sinusitis (51%) and control (58%) patients who reached full-strength dosages of nonfungal allergens were also similar.

Review of the Literature on Subcutaneous Immunotherapy With Fungal Allergens

Thirteen citations were identified from our MEDLINE and 66 from our PubMed searches. The 2 searches consisted of a total of 50 distinct publications. Abstracts were read for each citation. The 22 citations in which allergen immunotherapy and allergic fungal sinusitis were cited in the abstract were reviewed in full. The remaining 28 articles were review articles, editorials, or studies irrelevant to our analysis. Eight of the 22 articles on allergen immunotherapy in allergic fungal sinusitis met inclusion criteria for this study. These articles included 7 of the reports on fungal immunotherapy for allergic fungal sinusitis by Mabry and colleagues.

Mabry and colleagues used doses of allergen based on "skin test end point titration," a technique that may result in lower concentrations of allergens in immunotherapy than those recommended in practice guidelines.²⁸ This method for immunotherapy has been previously described and critiqued by others.^{17,29,30}

We carefully reviewed the 7 reports by Mabry and colleagues summarizing their experience with allergen immunotherapy in 11 or more postoperative patients with allergic fungal sinusitis.¹⁷⁻²³ There were no reports in these studies to suggest that there were any serious short- or long-term untoward reactions to allergen immunotherapy in those patients.

Specifically, no systemic, severe local, or immune complex reactions were reported.

In a report of the clinical features of allergic fungal sinusitis by another group, fungal immunotherapy was administered to 11 of 20 patients.¹⁶ Only 4 of 11 were adherent to the prescribed regimen. Similarly, no complications were mentioned.

DISCUSSION

Because allergic fungal sinusitis is a chronic inflammatory reaction to fungi within the sinuses, there is reason for concern that the administration of concentrated fungal allergens in immunotherapy could be associated with untoward events. In this study, we assessed our experience and that in the published literature to determine the nature and severity of any reactions that occurred. We found no evidence that reactions to fungal immunotherapy were associated with more frequent or more severe reactions in patients with allergic fungal sinusitis than those experienced by patients with allergen extracts containing fungal allergens for garden-variety rhinosinusitis. Similarly, those patients receiving fungal immunotherapy had no more severe or frequent reactions with immunotherapy to pollen allergens. Thus, the fungal immunotherapy did not "prime" these patients for reactions to other allergens. In addition, we found no evidence of immune complex reactions during administration of the immunotherapy or during follow-up for up to 5 years after completion of the immunotherapy. Our experience seems to mirror that in the largest previously reported series of patients with allergic fungal sinusitis who received fungal immunotherapy by Mabry and colleagues because they noted only minor local reactions. Although maintenance doses of immunotherapy used in that series may have been lower than those used in our patients, their experience is informative and supports our observations with traditional doses of allergen immunotherapy.

Allergic fungal sinusitis is a chronic disease for which the optimal treatment regimen has yet to be determined. The experience of Mabry and colleagues suggests immunotherapy may be a useful adjuvant to surgery and corticosteroids. The information provided here suggests that clinical trials of high-dose, traditional immunotherapy with fungal allergens may proceed in patients with allergic fungal sinusitis without undue concern. However, because the number of patients treated has been small and 1 scientific presentation suggested that fungal immunotherapy administered before removal of fungal contents from the sinuses could worsen sinusitis, prudently administered controlled studies are essential to moving forward.¹⁰

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