

The role of itraconazole in recalcitrant fungal sinusitis

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ABSTRACT

Background: Oral itraconazole is an antifungal that has been shown to be of benefit to patients with allergic bronchopulmonary aspergillus (ABPA). It is hypothesized that itraconazole may similarly benefit patients with allergic fungal sinusitis (AFS), a disease similar to ABPA. This study was designed to evaluate the therapeutic response of itraconazole in patients with refractory chronic fungal sinusitis who have failed maximal medical and surgical therapy.

Methods: A retrospective chart review was performed of 23 patients with AFS and nonallergic eosinophilic fungal sinusitis treated with oral itraconazole. Charts were reviewed for patient demographics, comorbidities, allergies, fungal cultures, type of surgery performed, and amount of oral steroids used before and after itraconazole. All patients were given a 6-month dose of itraconazole (100 mg b.i.d.) when recurrence developed after surgery. Time to next recurrence, change in oral steroid use, and outcomes were noted. Liver function tests were taken at monthly intervals while on itraconazole.

Results: Twenty-three patients, 13 men and 10 women, were started on oral itraconazole for recurrent fungal sinusitis. Nineteen patients responded to the medication with a decrease in symptoms and fungal mucin/polyps on endoscopy. Three patients had to stop because of elevated liver enzymes. In the remaining 16 patients a decrease in oral steroid use was noted. In addition, 11 of the 16 patients are disease free to date at a mean follow-up of 15.7 months. No permanent complications occurred from the use of the medication.

Conclusion: Oral itraconazole may be of benefit to those patients with recalcitrant fungal sinusitis who have failed maximal medical and surgical therapy. Itraconazole may prolong the time to next recurrence and may enable the patient to significantly decrease or stop oral steroids.

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Key words: Allergic fungal sinusitis, eosinophilic fungal sinusitis, ESS, fungal recurrence, itraconazole, medical management, recalcitrant fungal sinusitis

Persistent refractory chronic rhinosinusitis is a distinguishing feature of patients with allergic fungal sinusitis (AFS) and nonallergic eosinophilic fungal sinusitis (NAFES). Despite maximal medical and surgical therapy, symptoms are often difficult to control with frequent relapses common. AFS occurs in the atopic and immunocompetent patient whereby fungi acting as antigens stimulate the immune system causing a chronic inflammatory pattern. AFS is diagnosed by the presence of¹ type one hypersensitivity to fungi,² nasal polypoidosis,³ characteristic CT findings,⁴ histological evidence of eosinophilic mucin without fungal invasion,⁴ and/or positive fungal stain or culture.¹ NAFES is similar to AFS without the hypersensitivity or allergy to fungi. Both are characterized by thick fungal eosinophilic mucin and massive polyposis. Histology is similar in both, characterized by the abundance of eosinophils, inflammatory cells, Charcot-Leyden crystals, and fungal hyphae.²

Treatment of AFS and NAFES consists of surgery and medical therapy. Typical medical therapy includes the use of nasal steroid sprays, oral steroids, and, occasionally, immunotherapy.^{3–5} Many patients require several courses of oral steroids to control the disease while others need long-term low-dose steroids.⁶ Surgery is performed when the medical therapy can no longer control the patient's symptoms. It is not uncommon for these patients to undergo multiple sinus surgeries in a period of sev-

eral years. Cody *et al.* reported repeated debridements in 56% of patients with AFS.⁷ Aggressive surgery allows for the bulk of the disease to be removed but patients continue to inhale millions of fungal spores every day and reactivation of the disease even in operated sinuses is common. Therefore, surgery is often followed by a long tapering course of oral steroids until the mucosal disease appears to reverse.^{8,9} Unfortunately, recurrence is known to develop shortly after the steroids are finished. With the known complications of long-term steroid therapy, an alternative to oral steroids is needed in the treatment of patients with refractory disease.

Oral antifungals have been proposed as a treatment option in patients with refractory chronic fungal sinusitis. Antifungals are thought to decrease the antigenic load thereby reducing the trigger for chronic inflammation. In steroid-dependent allergic bronchopulmonary aspergillus (ABPA), a disease similar to AFS, itraconazole has been shown to lower the oral steroid dose, improve pulmonary function, exercise tolerance and symptoms, and decrease IgE levels.¹⁰ It is hypothesized that the response to itraconazole in patients with ABPA is due to the decrease in pulmonary fungal load. Similarly, it is speculated that itraconazole may reduce the fungal load within the nasal cavity and improve the mucosal disease in patients with fungal sinusitis. In this study we publish our results using oral itraconazole in patients with refractory AFS and NAFES who have had maximal medical and surgical therapy including oral steroids and in whom the disease recurs despite all treatments.

METHODS

A retrospective chart review was performed of all patients diagnosed with AFS or NAFES between the years of 2003 and 2008 who were treated with oral itraconazole. Patients were classified as AFS according to the criteria set forth by Bent and

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Kuhn.¹ The diagnosis of NAFES was given to patients with nasal polyposis, positive fungal cultures, or hyphae on stain, eosinophilic mucin on endoscopy, and eosinophilia/Charcot-Leyden crystals on histopathology. A few patients who fulfilled all of the criteria of AFS but did not grow fungi on culture were classified as AFS-like. All patients had undergone both maximal medical (including multiple courses of oral steroids) and surgical therapy (including maximal ostial opening often with a modified Lothrop procedure) before the initiation of oral itraconazole.

Charts were reviewed for patient demographics and comorbidities, number and type of surgeries performed, medical treatment and duration (oral steroids), pathology, allergy testing, and fungal cultures. All patients were treated by the senior author (P.J.W.) with maximal surgical therapy followed by a 3-week course of oral prednisolone and any recurrence was subsequently treated with itraconazole at a dose of 100 mg b.i.d. for a minimum period of 6 months. No oral steroids were given while the patients were on itraconazole. The response and duration of itraconazole, time to next recurrence, change in oral steroid regimen, complications, and outcomes were noted. Nasal endoscopy was performed at each office visit during and after the itraconazole course and any evidence of fungal recurrence was noted. All patients had liver function tests performed before the start of itraconazole and monthly while on the medication. Only those patients who were found to have elevated liver function enzymes were taken off of the medication before 6 months. No patients were excluded from the study.

RESULTS

Twenty-three patients, 13 men and 10 women, were included in the study. Five patients had Samter's triad (aspirin sensitivity, asthma, and nasal polyps) and 11 patients had asthma alone. Allergy testing was performed in all patients; 13 tested positive with 10 positive for molds. AFS was diagnosed in 9 patients, NAFES was diagnosed in 13 patients, and a diagnosis of AFS-like was diagnosed in 1 patient. Twenty-one of the patients were referred after failing previous surgical therapy. On average patients had 4.5 prior surgeries (range, 1–21). All patients had pansinusitis diagnosed on CT scan (average Lund score, 21.1). Surgery was performed by the senior author (P.J.W.) in all patients. A modified Lothrop was performed in 14 patients and 9 underwent complete functional endoscopic sinus surgery. All had a concurrent canine fossa puncture to completely clear out the fungal disease in the maxillary sinus. Polyps and fungal mucous (peanut butter-like) were found in all patients at the time of surgery. The average age at time of surgery was 49 years (range, 23–69 years).

Fungal cultures were positive in 14 patients, with *Aspergillus* the most common fungi recovered (Table 1). Histopathology showed fungal hyphae in 5 patients without positive cultures. One patient had negative cultures and fungal stains.

Patients were placed on oral itraconazole when disease recurred after surgery (average time to initiation of itraconazole was 9 months postoperation). Nineteen (82.6%) patients improved initially on itraconazole. Four patients (two AFS and two NAFES patients) had no improvement of symptoms or fungal mucous/polyps on endoscopy. Three responders had to terminate the therapy because of elevated liver en-

Table 1 Species of fungus in patients that grew fungus from their sinuses

Patient	Disease	Fungal Cultures
1	AFS	<i>Aspergillus fumigatus</i> , <i>Alternaria</i> , <i>Penicillium</i>
2	AFS	<i>A. fumigatus</i>
3	AFS	<i>Alternaria</i> , <i>Aspergillus</i> , <i>Dreschlera</i>
4	AFS	<i>Rhizopus</i>
5	AFS	<i>Aspergillus</i> , <i>Curvularia</i> , <i>Cladosporium</i>
7	AFS	<i>Acremonium</i>
8	AFS	<i>Alternaria</i>
9	AFS	<i>A. fumigatus</i>
12	NAFES	<i>Penicillium</i> , <i>Scedosporium</i> , <i>A. niger</i>
14	NAFES	<i>A. Flavus</i>
15	NAFES	<i>Dreschlera</i>
17	NAFES	<i>Aspergillus</i>
18	NAFES	<i>Rhizopus</i>
21	NAFES	<i>Dreschlera</i>

AFS = allergic fungal sinusitis; NAFES = nonallergic eosinophilic fungal sinusitis.

zymes, which normalized once the treatment was stopped. One patient had a temporary rise in gamma glutamyl transferase and was able to continue therapy with close monitoring of liver function tests. The 16 patients who responded and completed the course of itraconazole showed a varying degree of symptom improvement including a decrease in the use of oral steroids and fungal mucin/polyps on endoscopy (Table 2). Twelve of the 16 patients who were on steroids either continuously or receiving frequent bursts before itraconazole were able to stop or decrease the amount of steroid use after treatment. Other than a rise in liver enzymes in the four patients mentioned previously, no other complications occurred.

Of the 16 patients who completed the course of itraconazole and responded, 11, to date, are recurrence free with an average follow-up of 15.7 months (range, 7–36 months). Five patients who initially responded recurred at an average time of 9 months (range, 5–20 months). Two recurrences responded to a second course of itraconazole and one underwent revision surgery (Table 2).

DISCUSSION

This study looks at the response of 23 patients with recalcitrant fungal sinusitis (AFS and NAFES) treated with oral itraconazole. The majority of the patients had a history of multiple sinus surgeries (average, 4.5) and required several courses of oral steroids to keep symptoms to a minimum. Itraconazole was offered as a treatment alternative after exhausting surgery and steroid therapy. With itraconazole, 19 of the 23 patients showed improvement in symptoms and endoscopy findings. Many were able to decrease the frequency of oral steroid use and others were able to get off steroids

Table 2 Summary of patients' comorbidities, clinical course, and outcomes

Patient	ASA Sensitivity	Asthma	No. of Prior Surgeries	Disease Class	Improved on IT	Time to Recurrence after IT (mo)	Follow-Up (mo) after IT	Elevated LFTs	Stopped due to LFTs	Steroid Bursts/Time (before IT)	Steroid Bursts/Time (after IT)	Comments
1	N	N	2	AFS	Y	5	26	N	N	12/63 mo	2/26 mo	Recurrence cleared up with second course of IT
2	N	N	3	AFS	Y	No recur	13	N	N	3/9 mo	0/13 mo	Improved, able to get off oral steroids
3	N	Y	3	AFS	N	N/A	4	N	N	N/A	N/A	No response
4	Y	Y	21	AFS	Y	6	12	N	N	0	1/12 mo	Recurred when stopped IT
5	N	Y	3	AFS	Y	No recur	14	N	N	Cont low dose +	0/14 mo	80% improved on IT
6	N	Y	9	AFS	N	N/A	5	N	N	N/A	N/A	Minimal response, recurred while on IT
7	N	Y	0	AFS	Y	No recur	8	N	N	2/12 mo	1/8 mo	Fungus and polyps cleared with IT
8	N	Y	2	AFS	Y	20	26	N	N	5/24 mo	2/26 mo	Recurrence cleared up with second course of IT
9	N	Y	2	AFS	Y	No recur	25	N	N	Continuous low dose	0/25 mo	Improved, able to get off oral steroids.
10	N	Y	4	NAFES	Y	No recur	14	Temp	N	11/44 mo	0/14 mo	Improved, able to get off oral steroids
11	Y	Y	6	NAFES	N	N/A	8	N	N	N/A	N/A	No response
12	N	Y	2	NAFES	Y	No recur	36	N	N	1/11 mo	0/36 mo	Improved on IT
13	Y	Y	1	NAFES	N	N/A	7	N	N	N/A	N/A	No response
14	N	N	4	NAFES	Y	No recur	28	N	N	1/10 mo	0/28 mo	Good response to IT, decreased fungal mucin, polyps and edema
15	N	N	4	NAFES	Y	N/A	N/A	Y	Y	N/A	N/A	Improved initially, but stopped due to elevated liver enzymes
16	N	Y	7	NAFES	Y	No recur	12	N	N	3/9 mo	0/12 mo	Improved, able to get off oral steroids
17	N	N	2	NAFES	Y	No recur	9	N	N	5/42 mo	0/9 mo	Improved on IT
18	Y	Y	6	NAFES	Y	5	29	N	N	4/18 mo	1/29 mo	Recurred when stopped, recurrence treated with surgery
19	N	Y	1	NAFES	Y	9	24	N	N	1/5 mo	2/19 mo	Improved on IT, recurred when stopped
20	N	N	2	NAFES	Y	N/A	N/A	Y	Y	N/A	N/A	Improved on IT, smell returned and fungal mucin cleared
21	N	N	9	NAFES	Y	N/A	N/A	Y	Y	N/A	N/A	Responded to IT but stopped due to elevated LFTs
22	N	Y	0	NAFES	Y	No recur	7	N	N	3/5 mo	1/7 mo	Improved on IT, but still needed oral steroids
23	Y	Y	2	AFS like	Y	No recur	7	N	N	7/45 mo	0/7 mo	80% improvement

IT = itraconazole; AFS = allergic fungal sinusitis; NAFES = nonallergic fungal eosinophilic sinusitis; LFTs = liver function tests.

altogether. Although recurrence still occurred in 5 of the 16 patients who responded to itraconazole, only 1 of those patient needed revision surgery and in 2 the recurrence was treated with a second course of itraconazole. This is a significant accomplishment in patients with AFS/NAFES where treatment is more often unsuccessful, frustrating both the patient and the surgeon.

Oral itraconazole has been proposed as an alternative to revision surgery and steroids in the management of patients with recalcitrant fungal disease. Although prospective randomized controlled studies are lacking, supportive evidence is found in a large retrospective review of 137 patients treated with itraconazole. Rains *et al.*, looked at 137 patients with AFS treated with high-dose itraconazole (400 mg/day $\times$ 1 month, 300 mg/day $\times$ 1 month, 200 mg/day $\times$ 1 month, or until clear by endoscopy).¹¹ In this study 69 patients (50.3%) had recurrence at an average time of 10.8 months and 17 (20.5%) required revision surgery. This study concluded that itraconazole reduced the need for oral steroids and repeat surgical debridement.

Controversy exists regarding the appropriate dose and duration of itraconazole to give. The dose given in the study by Rains *et al.* was significantly higher than the dose used in our study. The use of high-dose itraconazole is supported in a double-blind, randomized, placebo-controlled study looking at steroid-dependent ABPA treated with high-dose itraconazole.¹⁰ In the same article, an open-label study was performed using the lower itraconazole dose. With the lower dose a beneficial response was seen suggesting that the lower dose may be as effective and useful as maintenance therapy.

Known complications of itraconazole include elevated liver enzymes, congestive heart failure, nausea, rash, headache, malaise, fatigue, and edema (Janseen Pharmaceutica, Beerse, Belgium). In our study using the lower dose of itraconazole (200 mg/day), three patients were withdrawn from therapy because of persistent elevated liver enzymes. We had no other side effects or complications.

This study suggests that itraconazole can be considered in those patients with refractory disease that have disease that is recalcitrant to both maximal medical (oral steroid) and surgical treatment. There are obvious limitations to this study because of its retrospective nature, small numbers, lack of controls, and randomization. However, all of these patients had failed the recognized treatment regimes and showed a reasonable response to oral itraconazole. Large prospective randomized controlled studies are needed to further evaluate the role of itraconazole in AFS/NAFES.

CONCLUSION

In our study all patients recurred after maximal surgical therapy, which either entailed a complete functional endoscopic procedure with canine fossa puncture or trephine or modified Lothrop with canine fossa puncture or trephine followed by postoperative steroids. Itraconazole was offered as a last resort in management of these patients. Although concrete data are lacking supporting the use of itraconazole in patients with recalcitrant fungal sinus disease, it may benefit those patients who have exhausted all other treatment regimens. It appears that itraconazole can be used in the select patients who respond, as an alternative to oral steroids and repeat debridement. Because there is a risk for potential toxicity and drug interactions, its use must be monitored closely.

REFERENCES

1. Bent JP III, and Kuhn FA. Diagnosis of allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 111:580-588, 1994.
2. Ferguson BJ. Eosinophilic mucin rhinosinusitis: A distinct clinicopathological entity. *Laryngoscope* 110:799-813, 2000.
3. Ferguson BJ. What role do systemic corticosteroids, immunotherapy, and antifungal drugs play in the therapy of allergic fungal rhinosinusitis? *Arch Otolaryngol Head Neck Surg* 124:1174-1178, 1998.
4. Mabry RL, and Mabry CS. Allergic fungal sinusitis: The role of immunotherapy. *Otolaryngol Clin North Am* 33:433-440, 2000.
5. Schubert MS. Medical treatment of allergic fungal sinusitis. *Ann Allergy Asthma Immunol* 85:90-97, 2000 (quiz 97-101).
6. Allphin AL, Strauss M, and Abdul-Karim FW. Allergic fungal sinusitis: Problems in diagnosis and treatment. *Laryngoscope* 101:815-820, 1991.
7. Cody DT II, Neel HB III, Ferreiro JA, and Roberts GD. Allergic fungal sinusitis: The Mayo Clinic experience. *Laryngoscope* 104:1074-1079, 1994.
8. Kupferberg SB, Bent JP III, and Kuhn FA. Prognosis for allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 117:35-41, 1997.
9. Kuhn FA, and Swain R Jr. Allergic fungal sinusitis: Diagnosis and treatment. *Curr Opin Otolaryngol Head Neck Surg* 11:1-5, 2003.
10. Stevens DA, Schwartz HJ, Lee JY, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med* 342:756-762, 2000.
11. Rains BM III, and Mineck CW. Treatment of allergic fungal sinusitis with high-dose itraconazole. *Am J Rhinol* 17:1-8, 2003. □

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