

Refractory Allergic Fungal Sinusitis and its Medical Management in a Tertiary Hospital

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Abstract

Background: Allergic fungal sinusitis (AFS) is the most common form of fungal sinus disease with a high rate of recurrence rate despite the advent of advanced endoscopic sinus surgery and usage of steroids. Refractory AFS is defined as a condition of allergy due to fungal antigenic elements not amenable to surgical removal or prolonged medical management. Oral itraconazole is an antifungal agent that seems to be benefit to the patients with refractory AFS. Hence, this study was conducted to compare the outcome of AFS after addition of oral itraconazole to the treatment protocol.

Aim of the Study: The aim of the study was to evaluate the acceptance and usefulness of itraconazole, an oral antifungal drug, in the treatment of refractory AFRS.

Materials and Methods: A total of 84 patients with refractory AFS were included in this study. The medical records of these patients were retrieved from the medical records section and analyzed. A detail history of the AFS was elicited and demographic data were tabulated. Nasal endoscopy was done before and 3 months after the itraconazole therapy and the findings were classified according to Lund-Kennedy endoscopic grading system, Scoring from 7 to 10 was graded as severe; scoring from 4 to 6 was graded as moderate and 1 to 3 as mild grade. Itraconazole was administered in the form of capsule 100 mg 2 times daily for 3 months. Prior hepatic function and renal function tests were undertaken for all the patients. All the data were analyzed using standard statistical methods.

Observations and Results: Among the 84 patients, there were 52 (61.90%) males and 32 (38.09%) females with a male to female ratio of 1.6:1. The patients were aged between 18 years and 78 years with a mean age of 33.45 ± 4.15 years. Conversion of severe grade patients to mild grade following itraconazole therapy was note; post-treatment findings were severe in 5 patients, moderate in 1, and mild in 78 patients.

Conclusions: Itraconazole may be useful as an adjunct in the management of AFRS. However, more studies, including a prospective randomized clinical trial, are required to determine if itraconazole is effective in the management of AFRS.

Key words: Allergic fungal sinusitis, Functional endoscopic sinus surgery and allergy, Refractory Allergic fungal sinusitis, Rhinosinusitis

INTRODUCTION

The allergic fungal sinusitis (AFS) is defined as an allergic disease of the nasal cavity and paranasal sinuses triggered by fungal antigen and clinically characterized by polyposis; stringy allergic mucin and rhinorrhea. Its pathogenesis is due to atopy, continuous antigenic exposure, and inflammation all playing their roles in the perpetuation

of the disease. AFS is prevalent worldwide for the past two decades. The fungal species commonly believed to be involved are aerosolized environmental fungi of the dematiaceous species in an immunocompetent host.^[1,2] The patients with AFS have previous history of allergic rhinosinusitis. Nearly 7–12% of patients affected by chronic rhinosinusitis actually carry a diagnosis of (AFS). The prevalence of AFS is also impacted by geographic factors; literature shows the majority of sites reporting cases of AFS to be located in temperate regions with relatively high humidity.^[3] In view of the complicated pathophysiology of AFS a wide variety of management plans are being used such as certain major and minor criteria are used to define and diagnose AFS, endoscopic surgical removal of the disease from the sinuses by

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exploration and supportive medical treatment using steroids, immunotherapy, and antifungal chemotherapeutic agents.^[4,5] Any attempt to control this disease by not or partially treating the underlying causes is likely that the patients would have a high rate of residual disease resulting in refractory AFS.^[6,7] Hence, successful treatment of AFS consists of a treatment plan to account for each of the factors responsible for the establishment of the disease which would result in the best chance of long-term disease control. This multipronged approach to eradicate the AFS consists of complete removal of all fungal mucin (usually requiring surgery) and long-term prevention of recurrence through either immuno-modulation (immunotherapy and/or corticosteroids) or fungistatic antimicrobials. In addition, one has to consider various related issues in such an approach such as (1) as there are different forms of fungal sinusitis, and each requires a specific therapeutic regimen, targeted at the pathogen, (2) antifungal agents induced hepato- and neurotoxicity should be addressed, and (3) The cost factor should be kept in mind while prolonged usage is required; many newer antifungal drugs are extremely expensive. (4) There are a very few randomized controlled trials which able to validate various studies.^[8,9,10] Itraconazole inhibits the cytochrome P-450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes. Bent and Kuhn^[11] showed that many of the fungi in AFRS have *in vitro* susceptibility to itraconazole. They include *Aspergillus*, *Bipolaris*, *Alternaria*, and *Curvularia*. In this context, the present study was conducted to evaluate the acceptance and usefulness of itraconazole, as an oral antifungal drug in addition to steroid therapy, in the treatment of refractory AFRS.

MATERIALS AND METHODS

A total of 84 patients attending the outpatient department of Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, were included in this study. The medical records of these patients were retrieved from the medical records section and analyzed. An Institutional Ethical Clearance was obtained before commencement of the study.

Inclusion Criteria

1. Patients diagnosed with refractory AFS were included in the study
2. Patients of all age groups were included in the study
3. Patients of both genders were included in the study.

Exclusion Criteria

1. Patients who are immuno-compromised are not excluded from the study
2. Patients with acute hepatotoxicity or renal toxicity were excluded from the study

3. Patients with recent history of functional endoscopic surgery were excluded from the study.

All the patients diagnosed as refractory AFS alone were included, and detail history taking and demographic data were tabulated. Before starting the itraconazole diagnostic nasal endoscopy was done to grade the mucosal disease of the nasal cavity and paranasal sinuses. They were graded based on Lund-Kennedy endoscopic grading system^[12] [Table 1]. Scoring from 7 to 10 was graded as severe; scoring from 4 to 6 was graded as moderate and 1 to 3 as mild grade. Similarly, at the end of 3 months trial with itraconazole nasal endoscopy was done to observe the effectiveness of treatment. Itraconazole was administered in the form of capsule 100 mg 2 times daily for 3 months. Prior hepatic function and renal function tests were undertaken for all the patients. All the data were analyzed using standard statistical methods.

OBSERVATIONS AND RESULTS

Among the 84 patients, there were 52 (61.90%) males and 32 (38.09%) females with a male to female ratio of 1.6:1. The patients were aged between 18 years and 78 years with a mean age of 33.45 ± 4.15 years. The youngest patient was age 19 years, and the eldest patient was aged 64 years. The demographic data were analyzed and tabulated in Table 2. There was no statistical significance in the correlation of the observations with incidence of refractory AFS data studied.

Using Lund-Kennedy endoscopic grading system,^[12] the pre-treatment endoscopic findings and post-treatment (with itraconazole) endoscopic findings were correlated and tabulated in Table 3. Before treatment, there were 71 patients with severe endoscopic findings classified with Lund-Kennedy endoscopic grading, moderate grade was seen in 4 and mild in 9 patients. Post-treatment findings were severe in 5 patients, moderate in 1, and mild in 78 patients [Table 3].

DISCUSSION

AFS is being managed by a variety of methods which include pre-operative local steroid spray, systemic steroids,

Table 1: The Lund-Kennedy endoscopic grading system^[12]

Characteristics	Score definition
Nasal polyps	0=none; 1=confined to middle meatus; 2=beyond middle meatus
Discharge	0=none; 1=clear and thin; 2=thick and purulent
Edema	0=absent; 1=mild; 2=severe
Scarring	0=absent; 1=mild; 2=severe
Crusting	0=absent; 1=mild; 2=severe

Table 2: The age, gender, and demographic data of the study group (n=84)

Observation	Male-52 (61.90%)	Female-32 (38.09%)	P-value
Age			
18-38 years	17 (20.23)	11 (34.37)	0.214
39-58 years	21 (25)	12 (37.50)	
59-78 years	14 (16.66)	9 (28.12)	
Allergy			
Dust	25 (29.76)	13 (40.62)	0.310
Diet	14 (16.66)	7 (21.87)	
Dandruff	13 (15.47)	12 (37.50)	
Smoking	28 (33.33)	4 (12.50)	
Alcohol	21 (25)	1 (3.12)	
Profession			
Agriculture	15 (17.85)	9 (28.12)	0.101
Student	4 (4.76)	2 (6.25)	
House wife	8 (9.52)	5 (15.62)	
Transport	16 (19.04)	14 (43.75)	
Office goers	9 (10.71)	2 (6.25)	
Socio-economic group			
Low	22 (26.19)	10 (31.25)	0.182
Middle	17 (20.23)	13 (40.62)	
High	13 (15.47)	9 (28.12)	
Previous history FESS	28 (33.33)	19 (59.37)	0.113

FESS: Functional endoscopic sinus surgery

Table 3: The before and after treatment grading of the endoscopic findings in the study group (n=84)

Lund-Kennedy endoscopic grading	Pre-treatment -84 (%)	Post-treatment -84 (%)	P-value
Mild	9 (28.12)	78 (92.8)	0.015
Moderate	4 (4.76)	1 (1.19)	0.152
Severe	71 (84.52)	5 (5.955)	0.001

antihistamines, antibiotics, and local antihistamines for 6 weeks and followed by functional endoscopic sinus surgery. Itraconazole is being used by few authors as adjunct therapy of AFRS. However, very few studies are available in the form of prospective randomized clinical trials to determine if itraconazole is an effective method or not. To give a successful treatment for AFS, there is a need to arrange the treatment plan addressing each factor that is responsible for the propagation of this disease. The potent anti-inflammatory and immuno-modulatory effects of corticosteroids are suitable to control the recurrence. However, the optimal dose and length of steroid therapy are not clearly discussed in the literature.^[4,13] Long-term follow-up of AFS patients shows high recurrence despite prolonged usage of corticosteroids in these patients.^[10] Hence, another method of AFS therapy was systemic antifungal therapy that was suggested by authors using exclusively medical treatment.^[13,11] Hence, antifungal therapy often was used in an attempt to provide some degree of control over recurrence of AFS. Denning *et al.* studied initially the effect of systemic itraconazole in patients with allergic bronchopulmonary aspergillosis and

demonstrated a decrease in total immunoglobulin E.^[13] In his study itraconazole was used in six patients and found that they were able to decrease the amount of prednisone required to prevent disease relapse and progression. Later on Rains and Mineck^[12] using up to 400 mg of itraconazole/day and then tapering down to 200 mg/day over 3 months, showed no major side effects. The rise in liver enzymes was only in 4% of their patients. Itraconazole appears to have a modest benefit as an adjunct in the management of refractory AFS.^[12] However, Ferguson^[14] opines that the cost of treatment with itraconazole, limited available data in the literature, and potential drug-related morbidity due to hepatotoxicity of systemic antifungal therapy may limit the usefulness of this form of treatment for non-invasive fungal disease. The other side effects of itraconazole and fluconazole are cardiac dysrhythmias, hepatic dysfunction, urticaria, and anaphylaxis. In the present study, the numbers of patients before treatment were 71 patients with severe endoscopic findings classified with Lund-Kennedy endoscopic grading; moderate grade was seen in 4 and mild grade in 9 patients. There was dramatic conversion of severe grade patients to mild grade following itraconazole therapy; post-treatment findings were severe in 5 patients, moderate in 1, and mild in 78 patients [Table 3]. In a similar study by Hashemi *et al.*,^[15] the authors observed upgrading of clinical findings and quality of life, also imaging studies, and after 3 months of treatment Lund-Mackay score of computed tomography scan were found to be lowered.

CONCLUSIONS

Itraconazole may be useful as an adjunct in the management of AFRS. However, more studies, including a prospective randomized clinical trial, are required to determine if itraconazole is effective in the management of AFRS.

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