

# Efficacy of voriconazole in nonsurgical treatment of allergic and chronic granulomatous fungal rhinosinusitis: a preliminary study

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## Objective

Evaluate the effectiveness and safety of voriconazole in the non surgical treatment of allergic fungal rhinosinusitis (AFRS) and chronic granulomatous fungal rhinosinusitis (CGFRS). Also, we present our conservative approach for cases of chronic granulomatous fungal rhinosinusitis with skull base involvement.

## Patients and Methods

26 Patients with the diagnosis of AFRS (17 patients) and CGFRS (9 patients) have been treated with voriconazole for a period of 3 weeks in AFRS to three months in CGFRS.

## Results

All patients with AFRS have shown marked improvement both clinically and radiologically, recurrence occur in 6 cases, two patients improved medically, and 4 patient required endoscopic sinus surgery. From 9 patients with CGFRS, 6 patients improved completely and did not require surgery, three patients had persistent or residual disease and required surgical interference.

## Conclusions

Voriconazole is effective, and safe in treatment of AFRS as well as CGFRS. This is a preliminary study; further long-term studies are required for proper understanding of the strategies of this new treatment in fungal rhinosinusitis management.

## Keywords:

allergic fungal, antifungal, aspergillosis, fungal rhinosinusitis, granulomatous fungal rhinosinusitis, invasive fungal, sinusitis, voriconazole

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## Introduction

Allergic fungal rhinosinusitis (AFRS) is the most common form of fungal sinusitis [1]. AFRS is similar to allergic bronchopulmonary aspergillosis in the severe immune response to the fungus [2]. AFRS can cause up to 7% of chronic rhinosinusitis cases requiring operative interference [3,4]. A hypersensitivity reaction to airborne fungus growth within paranasal sinus elicited a fungal-specific immunoglobulin (Ig)E and IgG response [5]. The most common isolated fungus from AFRS patients' sinuses in India as well as Saudi Arabia was *aspergillus flavus* [6]. This hypersensitivity reaction leads to due to mucin production, sinus mucosa hypertrophy and polyp with subsequent sinus obstruction [7]. Immune response in AFRS could be modulated through local and systematic corticosteroids [8]. In refractory AFRS cases, systemic antifungal therapy should be considered [7,9–11].

Chronic granulomatous fungal rhinosinusitis (CGFRS) occur in immunocompetent patients, geographically common in India, Sudan, and Africa. CGFRS is characterized by submucosal inflammation with granuloma formation, rare hyphae, and extensive fibrosis. *Aspergillus flavus* is the most common

associated fungus [12]. Voriconazole (VRC) is fungicidal triazole showed significant activity in the treatment of invasive aspergillosis in comparison with amphotericin B with better success rate and less toxicity [13].

## Aim

Evaluate the effectiveness and safety of the use of VRC as a single line treatment in nonsurgical management of AFRS and CGFRS. Also, we present our approach for treatment of CGFRS with skull base involvement.

## Patients and methods

Twenty-six patients with the diagnosis of AFRS (17 patients) and CGFRS (nine patients) in the period from June 2011 to June 2016 have been treated with VRC for a period of 3 weeks (in AFRS) to 3 months in CGFRS. The institutional

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review board approved the study. Before inclusion in the study all patients were given written consents and had full explanation of the study process. Full history, clinical examinations, computed tomography (CT) scan, chest radiography, and complete blood work up (liver function test, renal function test, serum electrolyte, and blood glucose level) were done. Nasal endoscopy and biopsy was done for all study group and the excised tissues were sent for bacteriological and pathological evaluations. A sheet was done for every patient including history (demographic data, complaint, duration of symptoms, associated chest disease, previous nasal surgery), examination (clinical, endoscopic examination findings), and investigation (CT and MRI findings, type of fungus affection, immune status), received treatment, and outcome of the treatment. In this study inclusion and exclusion criteria is shown in Table 1.

## Treatment

### Route of administration

Route of administration was oral route in AFR and intravenous routine in CIFRS.

**Table 1 Criteria for into and exclusion from the study**

Entry (inclusion) criteria
Immunocompetent patients or controlled DM throughout the study
Fulfill Kuhn criteria
Total serum IgE concentration >400 IU/ml within 2 weeks before entry (in AFRS patients)
Completion of the treatment and follow-up
Exclusion criteria
Incomplete treatment and follow-up
Treatment with antifungal drugs >5 days within 3 months before treatment
Immunocompromised patients
Patients not fulfill Kuhn criteria
Pregnancy or lactation
History of hypersensitivity to azole compounds
Age <13 years and weight <40 kg
Inability to take oral medication
Use of corticosteroids

AFRS, allergic fungal rhinosinusitis; DM, diabetes mellitus; Ig, immunoglobulin.

**Table 2 Definition of response to voriconazole therapy**

Reduction in the computed tomography findings by 50% or more
Decrease in the total IgE concentration by 25% or more
Complete improvement of the extranasal fungal affection (for invasive fungal sinusitis). At least one of the following conditions
Absence of the allergic mucin on endoscopic examination
No or grade I ethmoidal polyps
Subjective improvement of nasal symptoms by visual analogue scale where 0 no symptoms and 10 complete nasal obstruction

AFRS, allergic fungal rhinosinusitis; Ig, immunoglobulin; <sup>a</sup>Patients with AFRS were considered to have had a response if they met the first two criteria and at least one of the conditions. Responses were assessed by comparing values at week 0 with those at week 16;

<sup>b</sup>Response criteria used for AFRS and IFS were the same, except that there was no extranasal affection in AFRS; <sup>c</sup>Relapse was considered with return of symptoms, or a 33% increase in the IgE concentration.

## Dosage

The oral dose used for AFRS was 200 mg/day, twice daily, for 1 week then once daily for 1–2 weeks usually for AFRS. The intravenous dose for CGFRS was 12 mg/kg as a loading dose, then 8 mg/kg for 3 months.

## Treatment follow-up

A follow-up during treatment with clinical evaluation and endoscopic examination (weekly) was done; also, CT scan has been carried out (every 4–8 weeks). A weekly monitoring of the patients liver and kidney functions and electrolyte level was done. Chest x rays were done every 3 months for 1 year. Assessment of subjective improvement of symptoms was performed at the 16 and 32 weeks. The follow-up period was ranged between 12 and 72 months (average 40.7 months in AFRS and 42.4 months in CGFRS). Any disturbance in liver function test lead to treatment discontinuation, then re continued when liver function testing return to normal measures.

## Response criteria

Response criteria for the study are defined in Table 2.

## Results

The study involved 26 cases (17 cases of AFRS and nine cases of CGFRS) treated at Mansoura University Hospital. The clinical duration of their complaint was 3.5 months to 1.5 years.

### Allergic fungal rhinosinusitis group data

The mean age was 37.8 years, 17 patients (six male and 11 female patients). Clinical presentation was nonspecific in the form of nasal blockage, nasal discharge, hyposmia, and headache. Proptosis was presented in five patients and excessive lacrimation in three patients. Asthma was present in two cases. AFRS was presented unilaterally in 13 cases and bilaterally in four cases. The ethmoid and maxillary sinuses were the most common affected sinuses followed by frontal and sphenoid.

### Chronic granulomatous fungal rhinosinusitis group data

Mean age was 39.1 years, nine immunocompetent patients (four male and five female patients).

Clinical presentation was headache in nine cases, nasal blockage (eight cases), nasal discharge (six cases), proptosis (four cases), ophthalmoplegia (three cases) and vision loss (one case). Most common affected sinuses were ethmoid, then sphenoid. Intracranial extension was presented in two cases. Facial nerve palsy was present in one case (not explained whether it is in the course of the disease or due to other aetiology).

#### Histopathological findings

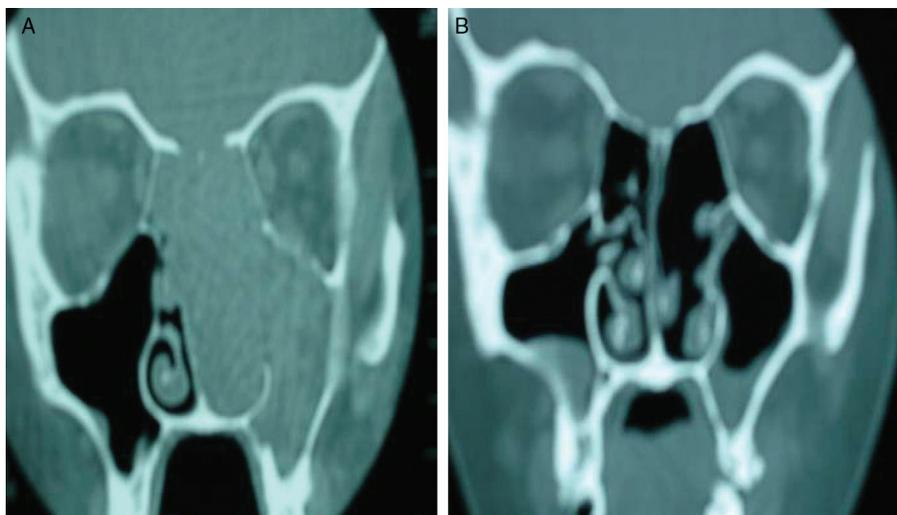
In AFRS, all cases showed extensive sheets of eosinophil's, edema, allergic mucin, no tissue invasion. The examination showed Charcot-Leyden crystals in 11 cases and fungal hyphae in 12 cases. In CGFRS, all cases showed diffuse submucosal granulomatous inflammation, giant cell reaction, superficial fungal invasion, and fibrosis.

#### Post-treatment evaluation

##### Allergic fungal rhinosinusitis

All patients with AFRS have shown marked improvement of both clinical, radiological (Fig. 1), with significant decrease of total IgE. The first case of AFRS was a 47 years old asthmatic patient who has nasal polyps, with pan sinus involvement and very high IgE; she was treated by a pulmonogist with oral VRC for 2 weeks. The patient nasal and chest condition had improved, post-treatment CT showed complete resolution of her sinus opacification. Recurrence occur in six cases, two patients improved with steroid (local and systematic), and four patient required endoscopic sinus surgery with improvement of all symptoms post operatively. In this study VRC was not given in the recurrent cases.

Figure 2



Showing a case with CGIFRS with ethmoidal roof erosion pre and post treatment with voriconazole.

##### Chronic granulomatous fungal rhinosinusitis

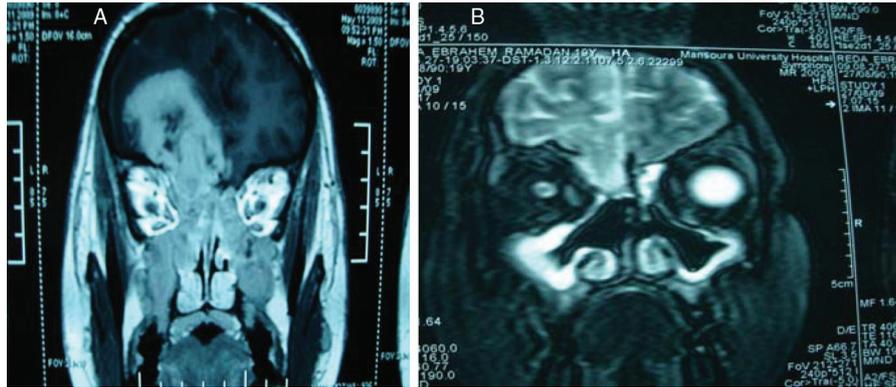
Six patients with CGFRS did not require surgery (Fig. 2), three cases had persistent or residual disease after VRC treatment and required surgical interference [two endoscopically and the other needed maxillectomy

Figure 1



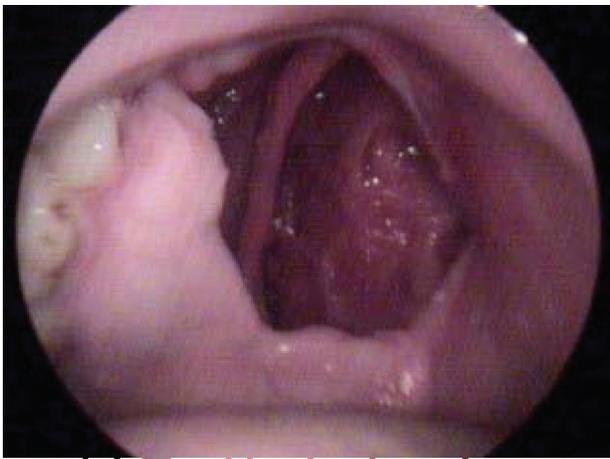
Showing a case with AFRS pre and post treatment with voriconazole, note the small ethmoidal osteoma.

Figure 3



Showing a case with CGIFRS with intracranial invasion pre and post treatment with intravenous voriconazole.

Figure 4



Showing a case with CGIFRS maxillectomy after failure of medical treatment with voriconazole.

(Fig. 3)]. The patient who had vision loss did not improve after treatment Fig. 4.

## Discussion

The prognosis and treatment varies among categories of fungal sinusitis, hence accurate classification is mandatory [14]. AFRS pathogenesis remains unclear. Fungal elements trapped in the sinus mucus have been suggested to stimulate IgE, IgG and IgA release [15]. Type I response is shown in AFRS due to high IgE level to the specific fungus. Nevertheless, a type III response is shown in AFRS due to IgG antibodies production [16]. Although most studies on AFRS suggested the integral fungus role in allergic reaction initiation. Alternatively other studies concluded that fungi may be saprophytic organisms and have not a role in the pathogenesis [17,18].

Invasive fungal sinusitis specific diagnostic criteria include mucosal thickening; presence of hyphae in

sinus mucosa, submucosa, blood vessel or bone; and, for CGFRS, hyphal forms within sinus tissue with granulomas containing giant cells [19]. CGFRS characterized by regional fungal tissue invasion with granulomatous or nonspecific chronic inflammation [20]. Tissue invasion by fungi on pathology is required for diagnosis of CGFRS. CT and MRI can show irregular bony destruction, soft tissues infiltration, or just mucosal thickening as in sinusitis [21]. Debridement and systemic antifungal therapy are the usual treatments of CGFRS [22]. The incidence of CGFRS in immunocompetent individuals is high in the Sudan and the Middle East [23].

As time is important in the development of the noninvasive fungal sinusitis, which may takes several years to develop. Also, in immunocompetent host, invasive form may represent a progress during time from noninvasive form [24]. A 'spectrum of disease' is proposed for paranasal aspergillosis with noninvasive form (aspergilloma or allergic type); semi-invasive form (local destruction and absence of tissue invasion); and invasive form (fungal tissue invasion either nonfulminant or fulminant) [25]. In our study many similarities were found between AFRS and CGFRS as geographical distribution, immunocompetent patients, aspergillus flavus association with the disease and concurrent occurrence. In many case during our surgical practice with AFRS a foci of invasion in the posterior maxillary wall, ethmoidal roof or lamina papyrea could be identified. This could not be attributed to the long duration of the disease but to a pathological progress of the disease toward CGFRS.

In AFRS, surgery is conducted to decrease fungal load in sinuses, reform mucousal clearance, and confirm diagnosis. It is well known that recurrence is common even with long standing steroid therapy. Most patients

treated (with surgery and steroids) had recurrence during 6 months after stoppage of steroids. These patients should be classified as chronic and probably not curable [26]. Extensive surgical debridement followed by the use of systemic antifungal agents was commonly done in the early attempts of AFRS treatment influenced by the fear that fungi within the paranasal sinuses indicated an early form of invasive fungal sinusitis.

Many studies recommend VRC as the line of choice in invasive aspergillosis. Central nervous system aspergillosis (mortality rate historically was over 90%) on VRC treatment showed over 33% success rate [27]. Although many studies considered azoles fungistatic agents, VRC exhibit fungicidal, time-dependent activity against aspergillus in-vivo pharmacodynamic studies [28]. Nevertheless, it was shown that the combination of VRC and caspofungin or amphotericin B and itraconazole might represent a great progress in invasive skull base aspergillosis treatment [29].

In clinical practice no strict line between invasive and noninvasive form of fungal rhinosinusitis, and although the use of VRC was indicated only in the invasive form, oral VRC was used in a study for 6 months duration for treatment of case of chronic invasive fungal sinusitis, which revealed atypical findings and the diagnosis of AFRS was allergic postulated. The oral VRC was given in the first 3 months at 200 mg twice daily, then once daily in the other 3 months [30]. Other study showed a case of noninvasive maxillary sinus aspergillosis transferred to invasive form after 5 years, in the form of intraorbital and posterior maxillary wall destruction which necessitates complete excision of the orbital contents and intravenous VRC was given for 6 weeks (140 mg daily), followed by oral VRC (150 mg daily) and itraconazole (400 mg daily) [31]. As regard VRC dosage reports showed wide variability and controversies depending on disease severity and institution protocols from 3 months to less than 15 months. In this study the duration of treatment was applied according to safety and severity of the pathology (3 weeks in AFRS and 3 months in CGFRS), these duration and dosage protocols may need further study and reevaluation.

According to international guidelines VRC was recommended as the first line treatment for acute invasive aspergillosis. However, invasive fungal sinusitis is rare, and only limited reports have described the clinical course of invasive fungal sinusitis treatment with new antifungal agents.

Whereas, seldom if any reports document antifungal agents use in treatment of AFRS (the most common form of fungal sinusitis) have been found in literature.

The increasing volume of literature on aspergillus sinus infection is confusing and a new scheme of classification is required as many studies postulated different aspects of the disease without absolute immunological or pathological guidelines. Nevertheless, the previous literature did not explain whether the difference represent various immunologic reaction, stage of disease, or different fungal load and species. As shown, CGFRS represent a progression of disease through a spectrum of abnormal immunologic reaction from fungal antigens atopy to invasive fungal process. The host's response to the fungal antigen load is documented through abnormal immunologic parameters detection (elevated immunoglobulin levels and precipitating antibodies). Hence, in this study the usage of VRC in allergic fungal sinusitis can be justified by the absence of strict and obvious guidelines whether immunologically, pathologically or even chronologically between safe and unsafe fungal sinusitis.

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## Conclusion

In our study, VRC was effective, successful, and safe in treatment of CGFRS (without surgical interference in six cases, three cases require surgical treatment) as well as in AFRS (without surgery or steroid in 11 cases), six recurrent cases have been shown during the follow-up period. Mechanism of systemic antifungal treatment in allergic disease is still questionable. Many similarities were found between AFRS and CGFRS as geographical distribution, aspergillus flavus association with the disease and concurrent occurrence in many cases. This is a preliminary study, other studies are required for studying this new modality of treatment as regarding dosage, benefits in recurrence prevention, and also whether it is a primary line of treatment in AFRS or it is held for resistant cases.

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**Conflicts of interest**

There are no conflicts of interest.

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