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ORIGINAL ARTICLE

Should Voriconazole be the Primary Therapy for Chronic Invasive Sinus Aspergillosis (CISA)?

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ABSTRACT

Introduction: Invasive sinus aspergillosis infection has been reported with increasing frequency in the last decade, especially, in immunocompromised patients with chronic invasive sinus aspergillosis (CISA). The gold standard for treatment has been wide surgical debridement, intravenous administration of antifungal agents, such as amphotericin B, but the prognosis remains poor. Newer antifungal agents are being tried but no standard treatment option with new antifungal agents has yet been established for chronic invasive fungal sinusitis. Therefore, we undertook this study to evaluate the efficacy of voriconazole in patients of chronic invasive sinus aspergillosis.

Materials and methods: This study is a prospective randomized unblinded study with primary aim of evaluating the feasibility and effectivity of voriconazole in patients of chronic invasive sinus aspergillosis with intraorbital or intracranial extension, and secondarily to compare voriconazole with amphotericin B therapy in patients with chronic invasive sinus aspergillosis.

Observations and results: Thirty-three patients who fulfilled the eligibility criteria were included in this study. There were 18 patients enrolled in group I who received amphotericin therapy and 15 patients in group II who received voriconazole therapy. Out of 33 patients, 9 patients had complete response, 10 had partial response, in eight patients disease became stable and there were seven failures. Overall 50% patients had a successful outcome in group I, whereas 60% had a successful outcome in group II receiving oral voriconazole. On comparing only in extradural group, 5/10 had a successful outcome in group I receiving amphotericin B, whereas 8/12 (66.7%) had a successful outcome in group 2 receiving voriconazole. There was significant difference between adverse reactions of the two drugs, with amphotericin B having a significant renal and cardiotoxicity as compared to voriconazole; though patients on voriconazole developed skin rashes which were transient and disappeared on completion of the therapy.

Conclusion: The present series demonstrates that oral voriconazole can be the primary line of therapy in chronic invasive sinus aspergillosis in carefully monitored immunocompetent cases. Multicentric, randomized studies are required to define disease definition, duration and successful outcome.

Keywords: Chronic invasive sinus aspergillosis, Treatment, Amphotericin B, Voriconazole.

INTRODUCTION

Invasive sinus aspergillosis infection has been reported with increasing frequency in the last decade, especially, in immunocompromised patients.[1,2] Recently, chronic invasive sinus aspergillosis (CISA) is being reported in immunocompetent patients at an increasing rate, while most of these cases are being reported from the Middle East and Indian subcontinent but cases are being increasingly encountered from North America and elsewhere also.[3] The gold standard for treatment has been wide surgical debridement, intravenous administration of antifungal agents, such as amphotericin B.[4] However, the prognosis remains poor, partly because of strong side effects of amphotericin B, sometimes not allowing its long-term administration. Newer antifungal agents are being tried with higher efficacy and lesser side effect.[5] However, no standard treatment option with new antifungal agents has yet been established for chronic invasive fungal sinusitis. Therefore, we undertook this study to evaluate the efficacy of voriconazole in patients of chronic invasive sinus aspergillosis.

MATERIALS AND METHODS

This study is a prospective randomized unblinded study conducted in the Department of Otolaryngology, Postgraduate Institute of Medical Education and Research, Chandigarh, India with primary aim of evaluating the feasibility and effectivity of voriconazole in patients of chronic invasive sinus aspergillosis with intraorbital or

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intracranial extension, and secondarily to compare voriconazole with amphotericin B therapy in patients with chronic invasive sinus aspergillosis.

DEFINITION

Chronic invasive sinus aspergillosis (CISA) was defined as histologically or microbiologically confirmed sinus infection with Aspergillus species along with incidence of fungal invasion of the sinus wall, orbit, facial soft tissue or presence of intracranial extension. Patients with compromised immune function and those not tolerating or affording voriconazole were excluded from the study. The patients underwent a detailed clinical history and examination, computerized tomography of nose and paranasal sinuses and MRI in cases with intracranial extension. Endoscopic debridement with the aim to have the specimen for mycological examination, included fungal smear and fungal culture, and histopathological examination for evidence of tissue invasive. All the patients with histopathological clinical or radiological evidence of chronic invasive sinus aspergillosis were included in the study. All the eligible candidates were randomly divided into two groups. Group I received conventional amphotericin B in the dose of 1 mg/kg/body weight once a day up to a maximum total dose of 2.5 mg or liposomal amphotericin B. Group II received oral voriconazole in loading dose of 400 mg 12 hourly in adults and 20 mg 12 hourly in children for two doses and then a maintenance dose of 200 mg 12 hourly in adults and 100 mg 12 hourly in children. The patients were followed up at the end of therapy for 14 weeks. The end point in this study was taken as outcome in terms of radiological and clinical response of the patient after withdrawing of voriconazole for 12 weeks. Outcome was taken in terms of clinical improvement and radiological resolution of the disease.

Outcome	*Clinical improvement + radiological resolution*
Complete resolution (CR)	Clinical improvement + 79% resolution of lesion
Partial response (PR)	Clinical improvement + 750% resolution of lesion
Stable response (S)	Not much clinical improvement + < 50% resolution of lesion
Failure (F)	Worsening of disease

OBSERVATIONS AND RESULTS

Thirty-three patients who fulfilled the eligibility criteria were included in this study. There were 18 patients enrolled in group I who received Amphotericin therapy and 15 patients in group II who received voriconazole therapy. Out of the 33 patients, 23 (69.7%) were males and 10 (30.3%) were females within age group of 22 to 56 years with a mean of 36.26 ± 8.82 years. The presenting signs and symptoms in these patients are shown in Table 1.

Headache was the most common symptom followed by ptosis, nasal obstruction, proptosis, soft tissue swelling, diplopia and periorbital pain.

Sphenoid sinus was most commonly involved followed by ethmoids and maxillary. A total of 13 patients had intraorbital involvement and 11 had intradural extension (Table 2).

OUTCOME

Table 3 shows the outcome of the patients in both the groups receiving therapy.

Out of 33 patients, nine patients had complete response, 10 had partial response, in eight patients disease became stable and there were seven failures in total. The detailed break up is shown in Table 3. CT scans of complete resolution (CR), partial response (PR), stable response (S), failure (F) are shown in Figures 1 to 4 respectively.

For the sake of comparison, all patients without any intracranial extension were considered as extradural and

Table 1: Sign and symptoms

Symptom	*No. of patients*	*Age (%)*
Headache	18	54.5
Ptosis	15	45.5
Nasal obstruction	14	42.4
Proptosis	12	36.4
Soft tissue swelling	10	30.3
Diplopia	10	30.3
Periorbital pain	7	21.2

Table 2: Radiological involvement by the disease

Sinus	*No. of patients*	*%*
Maxillary	12	36.3
Ethmoid	15	45.4
Sphenoid	21	63.6
Frontal	1	0.03
All sinuses	1	0.03
Intraorbital	13	39.4
Intradural	11	33.3

Table 3: Outcome in both the groups

	Group 1 (n=18)	*Group 2 (n=15)*
CR (n = 8)	4 (22.2%)	4 (26.7%)
PR (n = 10)	5 (27.8%)	5 (33.3%)
S (n = 8)	5 (27.8%)	3 (20%)
F (n = 7)	4 (22.2%)	3 (20%)

Complete resolution (CR), Partial response (PR), Stable response (S), Failure (F)

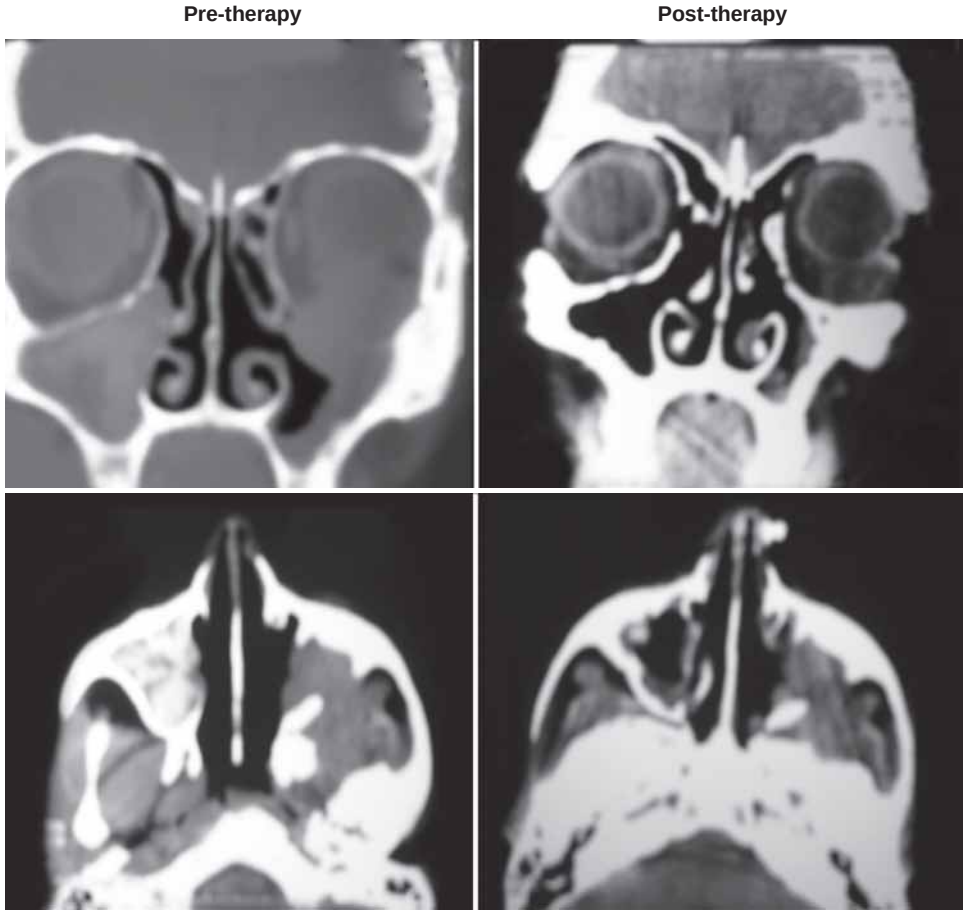

Fig. 1: Complete resolution (CR)

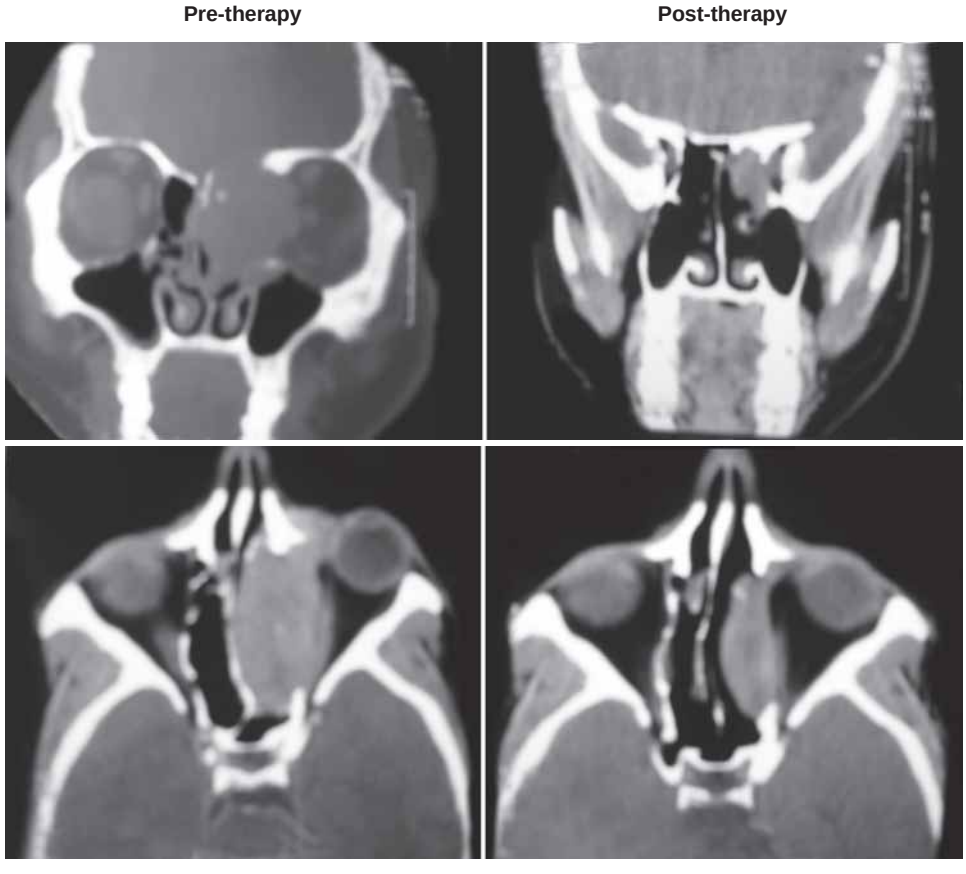

Fig. 2: Partial resolution (PR)

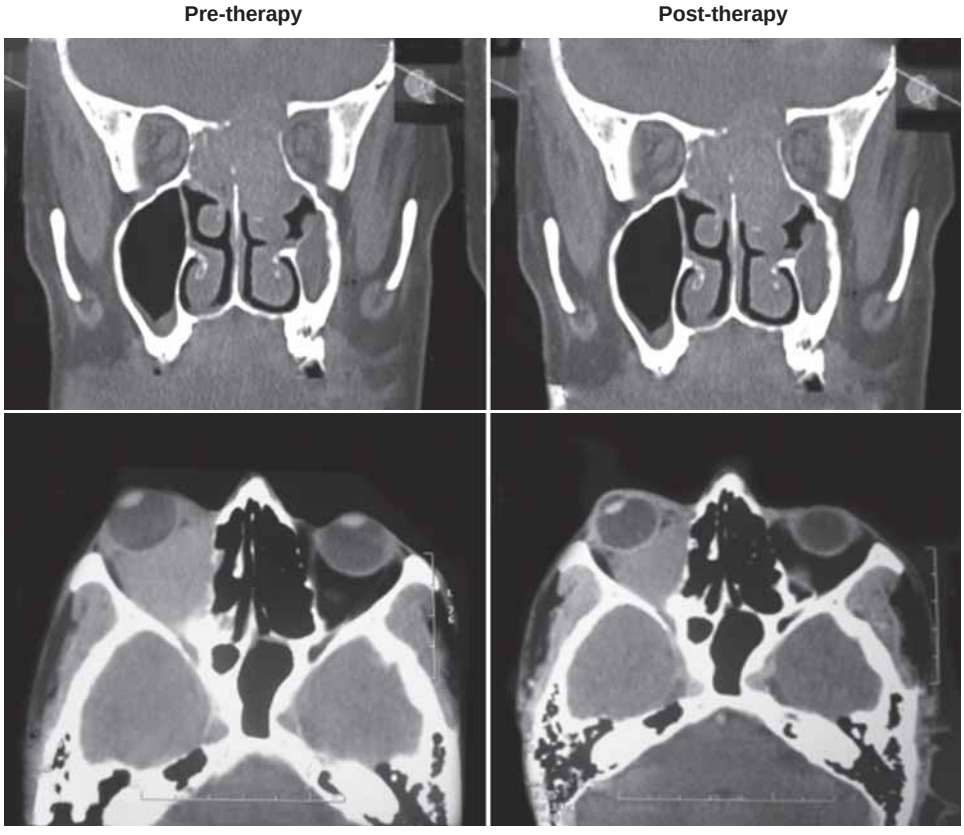

Fig. 3: Stable response (S)

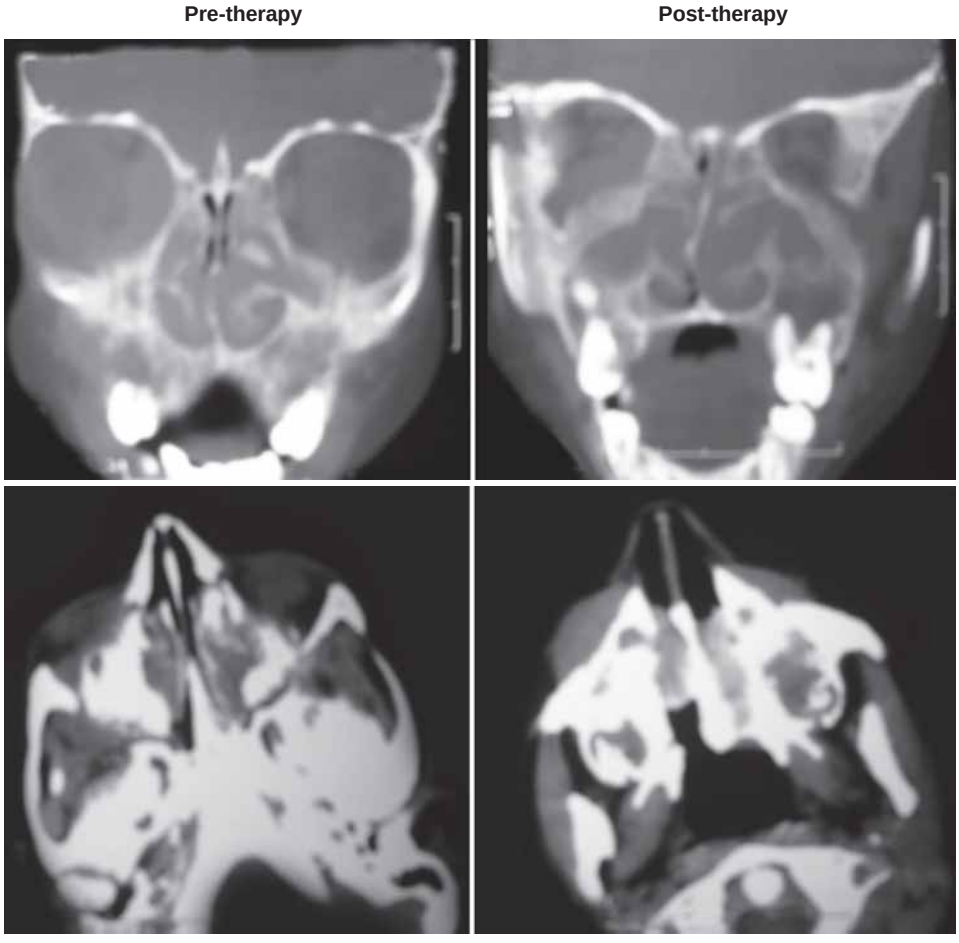

Fig. 4: Failure (F) to therapy

the outcome compared between the two groups is shown in Table 4. Overall 50% patients had a successful outcome in group I, whereas 60% had a successful outcome in group II.

On comparing only in extradural group, 5/10 had a successful outcome in group I receiving amphotericin B whereas 8/12 (66.7%) had a successful outcome in group II, receiving voriconazole (Table 5).

We divided the adverse reactions/events to these two drugs into five categories for the sake of comparison: Visual disturbances (VD), skin rashes, renal toxicity, hepatotoxicity and cardiotoxicity. It was found that there was significant difference between adverse reactions of the two drugs with amphotericin B having a significant renal and cardiotoxicity as compared to voriconazole, though patients on voriconazole developed skin rashes, which were transient and disappeared on completion of the therapy (Table 6).

DISCUSSION

Aspergillus species are the most common cause of fungal rhinosinusitis worldwide.[6] Invasive fungal sinusitis comprises of three subcategories: acute invasive, chronic invasive and granulomatous.[6] The acute or fulminant invasive is marked by vascular hyphal invasion, hemorrhage and infarction and a predilection for the immunocompromised host.[7] The granulomatous form has been described among immunocompetent patients in oral tropical regions in whom noncaseating granulomas are common and *A. flavus* is the predominant pathogen.[1,8-10] But nongranulomatous aspergillosis invasion of the sinus wall in the absence of clinically significant immunodeficiency has also been reported.[11,12] *A. flavus* is the most commonly isolated species from the environmental samples in areas where granulomatous fungal sinusitis predominates[13,14] probably due to the tropical climate, which also promotes a microaerophilic sinus environment conducive to the growth of *A. flavus*[1] as was seen in our series. Amphotericin B therapy has been the gold standard treatment for invasive sinus aspergillosis in spite of a poor prognosis, partly because of strong side effects of amphotericin B which prevents its long-term administration. New antifungal agents have recently been developed with lesser side effects like voriconazole. Voriconazole is a second generation triazole with a broad spectrum of antifungal activity against candida, aspergillosis, cryptococus and other species with superior effectiveness for invasive aspergillosis as compared to amphotericin B.[15] The optimum duration of antifungal drug administration for chronic invasive fungal sinusitis is controversial and reports vary widely, depending on the severity of the disease and institution from 2 months to more than 15 months.[16-18] In a review by Webb and Vikram on chronic invasive sinus aspergillosis in immunocompetent hosts, they found that treatment failure and mortality were not associated with degree of surgical intervention. But patients receiving azoles with activity against aspergillosis (i.e. voriconazole) alone or in combination with Amphotericin B survived more often, compared to patients receiving amphotericin B alone. In our series, 50% patients receiving amphotericin B had a successful outcome, whereas it increased to 60% in patients receiving voriconazole. In patients with extradural disease, 50% patients improved on amphotericin B in comparison to 66.7%, though the fisher exact test value is not significant, probably due to the small sample value. The patients having intracranial extension did not do well on voriconazole in our series. This could be most probably due to the shorter duration of voriconazole (3 months duration). A treatment of 6 to 12 months is being advocated in skull base aspergillosis these days.[16,17] There were significantly increased number of adverse nephrotoxic and cardiotoxic events in patients on amphotericin as compared to voriconazole in this series. Though 3 patients developed skin rashes on voriconazole, they were transient and did not hamper the administration of voriconazole to the patients and disappeared after the stopping of the drug. This study has its own limitation with a small sample size

Table 4: Successful outcome in both groups

	Group I	*Group II*	*p-value (Chi-square test)*
Extradural	10 (55.6%)	12 (80%)	0.138
Intradural	8 (44.4%)	3 (20%)	
Successful outcome	9 (50%)	9 (60%)	0.556

Table 5: Successful extradural outcome in both the groups

	Group I	*Group II*	
Successful extradural	5 of 10 (50%)	8 of 12 (66.7%)	0.666**

** Fishers exact test

Table 6: Adverse reactions to therapy in both groups

	Group I	*Group II*	*P-value (Chi-square test)*
VD (n = 6)	2 (11.1%)	4 (26.7%)	0.375**
Skin (n = 3)	0	3 (20%)	0.083**
Renal (n = 11)	11 (61.1%)	0	< 0.001
Hepato (n = 5)	2 (11.1%)	3 (20%)	0.639**
Cardio (n = 14)	13 (72.2%)	1 (6.7%)	< 0.001
Total ADR	17 (94.4%)	6 (40%)	0.001**

** Fishers exact test

for individual group but still has established the efficacy of voriconazole viz-a-viz amphotericin. There were comparable success rates of treatment with voriconazole, in fact having more success than amphotericin B in the extradural group and significantly lower adverse reactions with voriconazole.

CONCLUSION

The present series demonstrates that oral voriconazole can be the primary line of therapy in chronic invasive sinus aspergillosis, in carefully monitored immunocompetent cases. Multicentric, randomized studies are required to define disease definition, duration and successful outcome. More toxic drugs like amphotericin B should be reserved in cases failing to first line of therapy.

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