Comparison of Efficacy of Amphotericin B and Itraconazole in Chronic Invasive Fungal Sinusitis

Rupa Mehta · Naresh K. Panda · Satyawati Mohindra ·
Arunaloke Chakrabarti · Paramjeet Singh

Received: 12 July 2010 / Accepted: 26 December 2011 / Published online: 6 January 2012
© Association of Otolaryngologists of India 2012

Abstract Management of invasive fungal sinusitis includes both surgery and antifungal chemotherapy. To compare the efficacy of amphotericin B and itraconazole used alone in the management of chronic invasive fungal sinusitis. A prospective randomized unblinded study was conducted in the Department of Otolaryngology, Postgraduate Institute of Medical Education and Research, Chandigarh, India during December 2006 to June 2008. 26 immunocompetent patients were randomly divided into two groups—group A—received amphotericin B and group I—received itraconazole in conventional doses. The response to treatment was judged on the basis of symptomatic and radiologic resolution. Seven patients had complete cure (5/16—gr I; 2/10—gr A); Eleven patients had persistent disease (7/16—group-I; 4/10 in group A); four relapses were noted (3/16 in group I and 1/10 in group A); 3 deaths occurred; one patient was lost to follow up. Relative risk analysis did not show any statistically significant difference between the two drugs as regards their efficacy. Itraconazole and amphotericin B both have been found to be equally efficacious in the management of

invasive fungal sinusitis. Itraconazole however, has fewer side effects compared to amphotericin B.

Keywords Invasive fungal sinusitis · Immunocompetent · Antifungal agents

Introduction

Chronic invasive fungal sinusitis initially thought to affect only the diabetics and immunosuppressed and is being increasingly recognized in young healthy immunocompetent persons. Because of its potential to invade surrounding vital structures like brain and orbit, the morbidity associated with the disease and the treatment has made it a major cause of concern. Surgical clearance of the disease and antifungal therapy are the mainstay of treatment. Though a variety of antifungal drugs exist and newer ones are being introduced regularly, the usual response rates of various drugs vary from 40 to 60% [1]. Amphotericin B, itraconazole and voriconazole are the most commonly used drugs for chronic invasive aspergillosis. Amphotericin B, a polyene, though considered the gold standard, is associated with various side effects. Various formulations of amphotericin B—liposomal amphotericin B, Amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion have been introduced in order to combat the various side-effects of amphotericin B. Among the azoles itraconazole and voriconazole have been found effective and have less side effects. Itraconazole and amphotericin B have been used as monotherapy, combination or sequential therapy in the management of invasive fungal sinusitis [2]. To our knowledge, none of the studies have compared itraconazole and amphotericin B as monotherapy in the management of chronic invasive fungal sinusitis.

R. Mehta · N. K. Panda (✉) · S. Mohindra
Department of Otorhinolaryngology, Postgraduate Institute
of Medical Education and Research, Chandigarh 160012, India
e-mail: npanda59@yahoo.co.in

A. Chakrabarti
Department of Medical Microbiology, Postgraduate Institute
of Medical Education and Research, Chandigarh 160012, India

P. Singh
Department of Radio Diagnosis, Postgraduate Institute
of Medical Education and Research, Chandigarh 160012, India

Patients and Methods

A prospective randomized unblinded study was conducted in the Department of Otolaryngology, Postgraduate Institute of Medical Education and Research, Chandigarh, India during December 2006 to June 2008. A prior clearance from the Institute Ethics I committee was obtained before commencement of the study.

Disease Definition

Diagnostic Criteria

1. chronic invasive granulomatous fungal sinusitis confirmed by diagnostic imaging, mycological and histopathological examination
2. *Immunocompetent Patients.* Patients were presumed to be immunocompetent if they had not received chemotherapy, steroids or other immunosuppressive agents and if they had not received a diagnosis of cancer, chronic liver disease, end stage renal failure, HIV infection or congenital immunodeficiency before the isolation of aspergillus or during the follow up period.

Exclusion Criteria

Patients with known allergy to amphotericin B and/or itraconazole were excluded from the study.

Data Record and Investigations

Demographic data along with a detailed history of all the patients were noted.

All the patients underwent a detailed general, systemic, otolaryngological and ophthalmological examination. A non contrast computed tomographic scan of the nose and paranasal sinuses was done in all the patients. MRI was advised in cases of intracranial extension. Fungal serology was performed initially and at the end of treatment to determine any relapse. A titre of 1:64 or a fourfold rise in titre was considered significant.

Procedure and Analysis

The standard treatment protocol for invasive fungal sinusitis involves both surgery (to reduce the fungal load) and antifungal chemotherapy. In this study surgery was used to remove the disease in all the cases except for those cases in which there was intraorbital intraconal involvement with intact vision. A limited excision was accomplished in these cases.

After making a clinical and radiological diagnosis of chronic invasive fungal sinusitis, all the patients underwent surgical debridement. The surgical specimen was sent for fungal smear and culture and histopathological examination.

The patients were then assigned randomly into two groups—group A and group I based on a computerized randomization table.

Group A received conventional amphotericin B in the dose of 1 mg/kg body wt once a day (total dose 2.5 g) or liposomal amphotericin B in the dose of 3–5 mg/kg body wt (total dose—5 g) Group I received itraconazole in the dose of 300 mg twice a day for 2 days followed by 200 mg twice a day for 6 months.

Follow up Protocols

The patients were kept on regular follow up for a period of 6 months and were monitored for any side-effects during the course of treatment. Group A patients underwent twice weekly blood tests (serum urea, creatinine and serum electrolytes); Group I patients had fortnightly monitoring of liver function tests. A check CT/MRI was done after every 6 weeks to monitor the response to therapy.

Outcome Measure

The response to therapy was judged on this basis of:

1. Symptomatic improvement
2. Radiological resolution

Recurrent disease: Patients who presented with (1) reappearance of clinical symptoms and signs after they had abated or (2) reappearance of radiological evidence of disease after they had resolved during therapy.

Statistical Analysis

All quantitative variables were estimated using measures of central location (mean, median and mode) and measures of dispersion (standard deviation and standard error). Their 95% Confidence intervals were also calculated. Qualitative variables were described as frequencies and proportions. Normality of data was checked using graphics (histograms, box and whisker plots). Chi-square test was used to find out any statistical association between categorical variables. Mann–Whitney *U* test and Kruskal–Wallis test were used for analysis of quantitative variables. All tests were two-tailed and *P* value <0.05 was taken as significant.

Results

Though Northern India is considered an endemic zone for invasive fungal sinusitis as incidence of invasive fungal sinusitis is on the rise. We had planned to study 40 patients (20 each group) initially. However only 26 patients could be enrolled.

All these patients were immunocompetent i.e., they did not suffer from diabetes, malignancy, had not received corticosteroids or immunosuppressive therapy and were HIV negative. All the patients had normal haematological and biochemical parameters prior to start of therapy. None of the patients had fever. Out of the 26 patients, 16 patients were administered itraconazole as the primary therapy; ten received amphotericin B. Statistical analyses revealed similarity in both the groups as regards disease distribution and host factors.

Patient Characteristics

Eleven patients were females (gr I—6; gr A—5) and 15 patients were males (gr I—9; gr A—6). Male to female ratio was 1.36:1

Age ranged from 11 to 67 years (mean age—33.19 years; median—32; mode 32). The presenting signs and symptoms are shown in Fig. 1.

One patient had frank Allergic Bronchopulmonary Aspergillosis (ABPA) while five others had occasional chest symptoms for which they were using local steroid spray.

Sinus Involvement

Unilateral sinus involvement was seen in 22 patients while four patients had bilateral involvement. Sinus involvement in descending order was—ethmoids (73.1%), maxillary

Table 1 Showing the pattern of involvement of sinuses

Affected sinuses	No of cases
Maxillary sinus only	3
Maxillary and ethmoid sinuses	3
Maxillary and sphenoid sinuses	3
Maxillary ethmoid and sphenoid sinuses	1
Maxillary ethmoids and frontal sinuses	1
Ethmoid sinus only	5
Ethmoids sphenoid	6
Ethmoids, sphenoid, frontal	1
Frontal sinus only	0
Sphenoid sinus only	0
All sinuses	1

(69.2%), sphenoid (57.7%), and frontal sinuses (15.4%) (Table 1).

Extension Beyond the Sinuses

Intraorbital involvement was seen in 22 patients (12 in group I, 10 in group A); (14—infraconal; 8—extraconal). Five patients had intracranial extension (3—extradural; 2—intradural).

The disease eroded posterolateral wall of maxilla and extended to infratemporal fossa in six (23.1%) patients. Subcutaneous tissue involvement was seen in 11 (42.3%) cases.

Orbital apex involvement was seen in 53.8% (14) patients (Bilateral—2; unilateral—12).

Mycological Examination

Fungal smear was positive in 15 patients (57.7%) (*Aspergillus fumigatus*—2, *candida* sp. us—1; *Aspergillus flavus*—11) (Fig. 2).

Fig. 1 Showing the various signs and symptoms in the patients

Fig. 2 Showing the results of fungal smear and culture

Histopathological Examination

All the patients had fungal rhinosinusitis chronic granulomatous variety. Submucosal invasion and granulomatous inflammatory response was seen in all the patients. Fungal hyphae were seen in histopathological specimen in 22 patients. Splendore hoeppli phenomenon was seen in four patients.

Radiological Investigations

Serial CT scans were done for all patients; MRI was done for seven patients. Homogenous soft tissue density in paranasal sinuses was seen in 23 patients while heterogeneity was seen in three patients. Bony erosion without sinus expansion with spread to contiguous regions was seen in 24 patients. Erosion of lamina papyracea, anterolateral and posterolateral walls of maxilla was most commonly seen. Intracranial extension of the disease most commonly occurred due to erosion of lateral wall and roof of sphenoid (parasellar extension of the disease); erosion of posterior table of frontal sinus was seen in one patient. Intraorbital extension of the disease most commonly occurred following erosion of lamina papyracea, roof of maxillary sinus and due to orbital apex involvement due to erosion of lateral wall of sphenoid sinus. Widening of superior and inferior orbital fissures was seen.

Management

All the patients were taken up for surgery endoscopic in 9 (56%), combined approach in 4 (25%) and open approaches in 3 (18.7%).

Revision surgery was performed in five patients (19.2%).

One patient was treated wholly on outdoor basis; other patients required hospital admission. There was significant difference in the duration of hospital stay between the two groups. (Group I—3–10 days; group A—22–90 days.)

One patient in group I was lost to follow up. Three patients succumbed to the disease; two of them while on therapy while one died approximately 1 month after discharge at home (exact reason not identified). Both the patients who died while on therapy had intracranial intradural extension of the disease and were given amphotericin B in the hospital. Despite receiving treatment the patients had a rapid downhill course; developed multiple brain infarcts and ultimately died. Relapse was noted in four patients; three in itraconazole group and one in amphotericin B group.

Limited excision of the disease was done in seven patients in whom there was unilateral or bilateral orbital apex involvement with preserved vision; one had primarily

subcutaneous tissue involvement; two had intracranial involvement and had a rapid downhill course after admission. The patient with only subcutaneous tissue involvement showed a remarkable response with 6 months of itraconazole therapy symptomatically and radiologically. Orbital exenteration was done in one patient who presented with frozen globe.

Follow up

The mean follow up period was 11 months. One patient in group I lost to follow up; three patients died—two while on amphotericin B therapy and the third patient died after completion of amphotericin B therapy and discharge (exact reason unknown). The two patients who died while on therapy had intracranial intradural extension of the disease and had developed multiple brain infarcts (basal ganglia and brainstem) while the third patient had intraorbital intraconal disease with intracranial extradural extension.

Outcome

The outcome of treatment was measured symptomatically and radiologically. When there is no evidence of disease symptomatically and radiologically, the disease is said to have been cured (Fig. 3). When symptomatic cure has been achieved and there is no evidence of active disease, or progression of disease but radiologically lesion persists though in a regressed form, then the disease is said to be persistent. In our study seven patients had complete cure (5/16—gr I; 2/10—gr A); 11 patients had persistent disease (7/16—group-I; 4/10 in group A); four relapses were noted (3/16 in group I and 1/10 in group A); one patient in group I lost follow up. Three patients died; two while on therapy and one due to unrelated cause 1 month after discharge. There was no statistically significant difference in the outcome of the patients between the two groups, though the difference in cure between the two groups was closure to significance ($P = 0.668$) (Table 2).

Relative risk analysis did not show any statistically significant difference between the two drugs as regards their efficacy.

Most of the patients in both groups had almost complete subjective symptomatic improvement at the completion of therapy. This did not necessarily correlate with radiological resolution of disease especially in cases of intraorbital intraconal disease.

Recurrence

Itraconazole was administered as the primary therapy in three out of the four patients who had disease recurrence; one patient received amphotericin B. All four recurrences

Fig. 3 Pre and Post operative computerized tomography picture of a patient treated with endoscopic surgical debridement and itraconazole therapy

Table 2 Showing the outcome of patients in the two groups

	Group I (16)	Group A (10)	<i>P</i> value
Cured	5	2	0.668*
Persistent disease	7	4	1.000*
Relapse	3	1	1.000*
Lost f/u	1	0	1.000*
Death	0	3	0.138*

* Not significant

had orbital apex involvement; one had intracranial extradural extension of the disease. Three were males; one was female. The duration of symptoms before presentation varied from 3 months to one and a half years. One patient had frank ABPA. All of them hailed from agricultural background. *Aspergillus flavus* was the agent isolated in all the four recurrences.

Adverse Effects

The various side-effects of amphotericin B and itraconazole noted in the patients are listed below in Table 3.

None of the patients had hypersensitivity to amphotericin B. Since most of our patients had no other associated comorbid illness and were not on any other drug therapy, drug interactions posed no problem with either amphotericin B or itraconazole. Liposomal amphotericin B was used

Table 3 Showing the adverse effects experienced in both groups

Group A (amphotericin B)	Group I (itraconazole)
Fever, chills, rigors, nausea, vomiting	Nausea, abdominal pain
Thrombophlebitis	Weight gain
Hypokalemia	
Deranged RFTs(raised urea and creatinine)	
Raised liver enzymes	

in five patients, when they could not tolerate conventional amphotericin B. However, its cost was a major prohibitive factor in our patients.

Hospital stay: There was a significant difference ($P < 0.01$) in hospital stay between group I (3–10 days) and group A (22–90 days).

The participant flow chart is provided in Fig. 4.

Discussion

There has been a paucity of studies on comparative efficacy of various antifungal drugs for invasive fungal sinusitis. The disease per se and its treatment may cause increased morbidity and mortality in young and middle aged people.

Fig. 4 Showing the participant flow diagram

We prospectively studied patients of chronic invasive fungal sinusitis to evaluate the efficacy of amphotericin B and itraconazole in the treatment and in the prevention of relapse. An attempt has also been made to study the epidemiological, clinical, radiological, mycological, histopathological features of the disease and correlate the various parameters. Ours is a tertiary referral centre and caters to the population of North India which is an endemic zone for this disease.

Since the number of patients in this study is small, the epidemiological parameters in this study might not be representative of the entire population. Slight male preponderance was noted in our study similar to other studies [3]. The male to female ratio in our study was 1.36:1. Young and middle age people were affected more in accordance with the other studies [3].

Environmental exposure also acts as a predisposing factor. In the present study, 21 patients had agricultural background; one patient dealt with old books. In other studies also, most of the patients were agricultural workers and manual labourers.

The mean duration between onset and presentation of the disease was 4 months (range—15 days to 8 years). In a study by Murthy et al. [4], the mean duration of disease at the time of presentation was 9.5 months (range 4 ± 48 months). Clancy and Nguyen [5] reported a mean delay of 24 months while Alrajhi et al. [6] reported a mean duration of symptoms of 18 months before diagnosis.

Proptosis (61.5%) was the most common symptom followed by nasal obstruction and discharge, facial swelling, headache, visual disturbances, diplopia. Alrajhi et al. [6] noted nasal obstruction in 87% of his patients followed by proptosis in 69%. Clancy and Nguyen [5] in their study noted proptosis in 52% of patients. As in previous studies reported from Sudan, Saudi Arabia and India, *Aspergillus flavus* was the most common isolate; *Aspergillus fumigatus* was isolated from two patients; *aspergillus candidus* was isolated from one patient.

Ethmoid sinuses were the most common sinuses involved in our study (73.1%) similar to other reports in literature [5, 6]. All the sinuses were involved in just one patient. Frontal sinus involvement was less commonly seen (in two patients). Isolated sphenoid sinus involvement has also been reported in few studies [7]. None of our patients however, had isolated sphenoid sinus involvement.

Orbital apex involvement was commonly seen (53.8%). This type of disease presentation deserves special mention as it serves as an easy portal of intracranial spread of disease.

There is a difference of opinion about the management of orbit in intraorbital spread of disease. Few recommend orbital exenteration to achieve surgical margins in spite of functional status of the eye [8]. Others recommend vision

sparing approach, i.e.,—conservative debridement with antifungal drugs [9, 10]. We used vision sparing approach in patient with intraorbital disease in whom the vision was preserved. Orbital exenteration was done in only one patient who presented with frozen globe.

Denning [11] treated 76 people with invasive aspergillosis with itraconazole (600 mg/day for 4 days followed by 400 mg/day) for a median of 46 weeks. 36% of participants had a complete or partial response, 4% were stable and 56% failed treatment or withdrew. Our results are also comparable though the number of patients is small.

One patient had associated ABPA. Concurrent occurrence of ABPA and AFRS has been reported in few studies [12, 13] but no study has yet reported simultaneous occurrence of ABPA and invasive aspergillosis. This again points towards fungal sinusitis being a continuous spectrum of disease.

Two patients in itraconazole group reported weight gain; weight gain has not yet been reported in any of the studies. None of the 16 patients had deranged liver function tests or hypersensitivity to itraconazole. Few studies have reported discontinuation of the drugs due to deranged liver function tests. Despite a long course of treatment the compliance of the patients was good with itraconazole. We used conventional doses of itraconazole (4–6 mg/kg body weight per day). Yamanoi et al. [14], has used high dose of itraconazole (16–24 mg/kg) in his study with few side effects. Due to erratic bioavailability of itraconazole serum drug concentration monitoring has been advised. Since all our patients were immunocompetent and did not have any comorbid illness, drug interactions did not pose any problem which becomes a significant consideration in post transplant patients on multiple drugs.

Chronic invasive fungal sinusitis can present in various forms—sino nasal. Sino-orbital, Sino naso orbital, sino orbito cranial, sinocranial, sino cutaneous. Out of these, sino orbital, sino naso orbital and sino cutaneous are the most common presentations. Intraorbital extension of the disease in chronic invasive fungal sinusitis occurs quite early in the course of the disease.

Patients with sinocutaneous disease present with induration and disc shaped swelling in the cheek and medial canthal region. Clearance in such situation requires external approach. Weber Ferguson and Caldwell luc are the most frequently used approaches. Patients with sinocutaneous disease showed excellent response to itraconazole.

Both amphotericin B and itraconazole had equal efficacy as per the results of our study. However, Itraconazole therapy required much shorter hospital stay compared to amphotericin B. It also has an added advantage of better tolerability and lesser side effects. Itraconazole can therefore be tried as first line therapy in invasive fungal sinusitis. The small number of patients is one of the limitations of the study.

Conclusion

Itraconazole and amphotericin B both have been found to be equally efficacious in the management of invasive fungal sinusitis. Itraconazole has fewer side effects compared to amphotericin B.

References

1. Stevens DA, Kan VL, Judson MA (2000) Practice guidelines for disease caused by *Aspergillus*. *Clin Infect Dis* 30:696–709
2. Panda NK, Saravanan K, Chakrabarti A (2008) Combination antifungal therapy for invasive aspergillosis: can it replace high-risk surgery at the skull base? *Am J Otolaryngol* 29:24–30
3. Siddiqui AA, Shah AA, Bashir SH (2004) Craniocerebral aspergillosis of sinonasal origin in immunocompetent patients: clinical spectrum and outcome in 25 cases. *Neurosurgery* 55:602–611
4. Murthy JM, Sundaram C, Prasad VSSV, Purohit AK, Ramamurti S, Laxmi V (2001) Sinocranial aspergillosis: a form of central nervous system Aspergillosis in South India. *Mycoses* 44:141–145
5. Clancy CJ, Nguyen MH (1998) Invasive sinus aspergillosis in apparently immunocompetent hosts. *J Infect* 37:229–240
6. Alrajhi AA, Enani M, Mahasin Z, Al-Omran K (2001) Chronic invasive aspergillosis of the paranasal sinuses in Immunocompetent hosts from Saudi Arabia. *Am J Trop Med Hyg* 65(1):83–86
7. Chopra H, Dua K, Malhotra V, Gupta RP, Harpreet P (2006) Invasive fungal sinusitis of isolated sphenoid sinus in immunocompetent subjects. *Mycoses* 49:30–36
8. Mauriello JA, Yopez N, Mostafavi R, Barofsky J, Kapila R, Baredes S, Norris J (1995) Invasive rhinosino-orbital aspergillosis with precipitous visual loss. *Can J Ophthalmol* 30:124–130
9. Adler SC, Isaacson G, Sasaki CT (1997) Invasive aspergillosis of the Paranasal sinuses and orbit: can you save the eye? *Am J Otolaryngol* 18:230–234
10. Massry GG, Homblase A, Harrison W (1996) Itraconazole in the treatment of orbital aspergillosis. *Ophthalmology* 103:1467–1470
11. Denning DW, Lee JY, Hostetler JS et al (1994) NIAID Mycoses Study Group Multicenter trial of oral itraconazole therapy for invasive aspergillosis. *Am J Med* 97:135–144
12. Shah A, Panchal N, Agarwal AK (2001) Concomitant allergic bronchopulmonary aspergillosis and allergic Aspergillus sinusitis: a review of an uncommon association. *Clin Exp Allergy* 31:1896–1905
13. Sher TH, Schwartz HJ (1988) Allergic Aspergillus sinusitis with concurrent allergic bronchopulmonary Aspergillus: report of a case. *J Allergy Clin Immunol* 81:844–846
14. Yamanoi T, Shibano K, Soeda T, Hoshi A, Matsuura Y, Sugiura Y, Endo K, Yamamoto T (2004) Intracranial invasive aspergillosis originating in the sphenoid sinus: a successful treatment with high-dose itraconazole in three cases. *Tohoku J Exp Med* 203:133–139