Original Article

# A comparative study of itraconazole in various dose schedules in the treatment of pulmonary aspergilloma in treated patients of pulmonary tuberculosis

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## ABSTRACT

**Introduction:** The optimal dose, duration, and efficacy of itraconazole in Indian patients of pulmonary aspergilloma (PA) are not clearly defined. Therefore, a study was carried out, to resolve these issues in diagnosed cases of PA complicating old treated patients of pulmonary tuberculosis. **Materials and Methods:** The study patients randomly received itraconazole either in a fixed dose schedule of 200 mg (group I), 200 mg twice daily (group II) or a variable dose schedule (group III), for 12 months. All the patients were followed up for the entire duration of the study for clinical, radiological, and immunological response. The side effects were recorded as and when reported by the patients and managed symptomatically. **Results:** A total of 60 patients were enrolled, 20, in each group. There were no intergroup differences with regard to age, sex, body weight, smoking status, alcohol intake, symptoms, Potassium hydroxide (KOH) mount, fungal culture, pattern of radiological lesions or anti-aspergillus antibodies (anti-Asp-Ab) titers. The radiological response was poor in group I patients, as compared to the other groups, at two months ($P < 0.05$). The dose of itraconazole was increased in five of the patients in group I due to poor response. A higher number of group II patients suffered side effects and the dose of itraconazole had to be decreased in three of these patients, but none of the patients on a variable dose schedule required a change in dose schedule. **Conclusion:** Thus, a weight-based variable dose schedule of itraconazole was found to be a more effective and safer modality in the management of PA than a fixed dose schedule.

**KEY WORDS:** Anti-aspergillus antibody, itraconazole, pulmonary aspergilloma

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## INTRODUCTION

Pulmonary aspergilloma (PA), a saprophytic form of aspergillosis, results from a growth of *Aspergillus* in damaged bronchopulmonary tissues, most commonly the residual tubercular cavities.[1] Recurrent or massive hemoptysis is the most frequent manifestation of the disease. Other symptoms include cough, dyspnea, malaise, weight loss, wheezing, chest pain, and/or fever. Many of the patients may remain asymptomatic for several years.

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Radiologically, PA usually presents as a single ball-like lesion or multiple ball-like lesions inside cavities, partially surrounded by a radiolucent crescent (Monod sign),[2] but early disease may present with recent thickening of the cavity wall and/or pleural thickening.[3] As most of these patients either do not expectorate or their sputa are negative for mycelia, the diagnosis of PA is mainly based on the detection of anti-aspergillus antibodies (anti-Asp-Ab) in their serum.[2,4]

Surgical resection is the only definitive mode of treatment for PA, but low respiratory reserve often makes it impossible.[5,6] Further, attempts to resect PA with multiple ball-like lesions, often referred to in the surgical literature as complex PA, has been associated with high morbidity and mortality. Bronchial artery embolization may be a useful life-saving measure in some patients with massive hemoptysis but re-bleeding is common and the measure is to be used at best as a short-term therapy, to stabilize the patient till other definitive therapy is instituted.[7] Direct

intracavitary installation of an antifungal agent through the endobronchial route or cavernostomy and radiotherapy has also been tried out with variable, but inconsistent results. Medical therapy has been traditionally considered to have limited activity in the treatment of PA, but it is the only hope of cure in times to come.

Among the antifungal agents, itraconazole is the most suited drug to deal with a chronic condition such as PA and indeed it is the most frequently used drug, being an orally administered agent, with low cost, high activity against *A. fumigatus,* and high tissue penetration into the lung. However, it works slowly and may not be useful in patients presenting with massive hemoptysis. Tsubura[8] has recommended a dose of 200 mg per day for six months, but Gupta *et al*.[9] have been able to achieve only partial success on such a dose schedule. The latter have argued that a low dose of the drug or inadequate duration of therapy may be responsible for this. Higher doses of itraconazole have been used around the world in the management of severe mycosis,[10,11], but Agarwal *et al*. have noted side-effects in about half of their patients on a dose of 400 mg/day.[12] Thus, the dose and duration of the drug to be used in PA are not clearly defined. It has been hypothesized that a fixed dose of the drug may not be optimal for every patient of PA, as it may be ineffective in overweight patients and too toxic in low-weight patients. Furthermore, 12 months of therapy may be more effective than six months.

Therefore, a study was carried out to define the optimal dose and duration of itraconazole therapy, based on the efficacy and tolerance of the drug, in diagnosed cases of PAs.

## MATERIALS AND METHODS

The intake for this prospective, randomized study was started in July 2012 and completed in December 2013. All old treated patients of pulmonary tuberculosis, with a disease duration of more than two years, reporting to the Outpatient Section of the Department of Respiratory Medicine, NIMS Hospital, Jaipur, with respiratory symptoms, along with ball-like lesions inside the cavities or a recent thickening of cavity wall in their chest x-ray/ computed tomography (CT) of the thorax were enlisted. The study methodology is briefly shown in Figure 1.

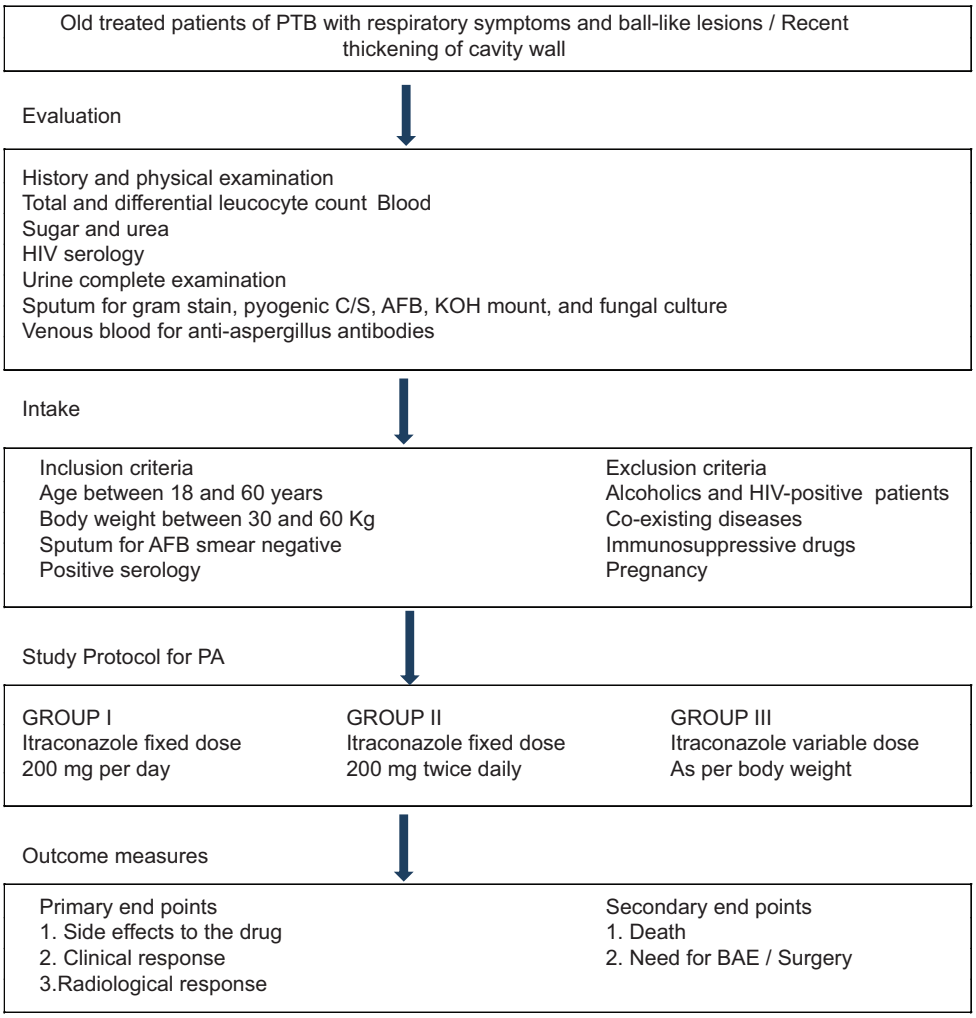


**Figure 1:** Consort diagram showing the study methodology

After careful clinical assessment these patients were subjected to laboratory investigations that included total and differential leucocyte counts, blood sugar and urea, human immunodeficiency syndrome (HIV) serology, complete urine examination, and sputum for Gram stain, pyogenic culture/sensitivity (C/S), and acid fast bacillus (AFB). Two additional morning sputa samples were collected and sent for KOH mount and fungal culture. Venous blood samples drawn from each patient were subjected to an estimation of anti-Asp-Ab as per the protocol used by Gupta *et al*.[4]

All PA patients of age between 18 and 60 years, body weight between 30 and 60 Kg, having two sputa smears negative for AFB, and positive serology (Anti-Asp-Ab titers >60 IU/ml), were included, however, pregnant women, alcoholics, HIV seropositives, and those having co-existing diseases, such as, diabetes mellitus, chronic renal failure, and chronic liver failure or those on immunosuppressive drugs were excluded.

## Study protocol

All the study patients were given a loading dose of itraconazole, that is, 400 mg per day (200 mg, twice daily) for three days and then randomly allocated to one of the three groups as under:

- GROUP I: Itraconazole in a fixed dose of 200 mg per day for 12 months
- GROUP II: Itraconazole in a fixed dose of 200 mg twice daily for 12 months
- GROUP III: Itraconazole in a variable dose schedule, as per body weight, for 12 months, that is, 200 mg/day for 30 – 39 Kg, 300 mg/day for 40 – 49 Kg, and 400 mg/day for >50 Kg

All the patients were followed up for the entire duration of the study for clinical and radiological response, at monthly intervals. Anti-Asp-Ab titers were estimated at two, six, and twelve months. Adverse effects were recorded as and when reported by the patients and managed symptomatically (chiefly lesupride 25 mg, every eight hours).

On the basis of the pattern of a radiological lesion, PA was classified as (a) Early PA: Recent thickening of the cavity wall and/or pleura; (b) Simple PA: One or two large, ball-like lesions inside the cavity/cavities, and (c) Complex PA: Multiple, small, ball-like lesions inside the cavities. The criteria for clinical response included control or decrease in the amount of hemoptysis, control or decrease in cough/expectoration, control or decrease in shortness of breath, and control of weight loss or increase in weight. The criteria for radiological response included a decrease in size or disappearance of the fungal ball and thinning of cavity wall. The clinical/radiological response was defined as good, partial or poor.

Those patients who showed poor clinical as well as radiological responses at two months were shifted to a higher dose schedule of itraconazole, but those patients who continued to suffer adverse effects in spite of symptomatic treatment were shifted to the lower dose schedule. All such patients, where the dose schedule had to be changed, were also followed and monitored as per the protocol of the study, but were excluded from the group analysis. However, these patients were included in the subsequent correlation analyses. Patients who continued to have massive hemoptysis (>100 ml/day) were referred for bronchial artery embolization (BAE). The primary endpoints included clinical response, radiological response, and adverse reactions. The secondary endpoints included death and BAE.

The data so obtained were tabulated and statistically analyzed using the student's t-test, the analysis of variance (ANOVA) test, and $\chi^2$ test or Fisher exact test, as applicable. The results were also subjected to multivariate analysis, if the difference between the variables on univariate analysis was highly significant ($P < 0.0001$).

The ethical clearance for the study was initially given by the SMS Medical College, Jaipur, and later, confirmed by the NIMS University, Jaipur. The study was registered with the Clinical Trials Registery (CTR) (CTRI/2013/02/003374/11/2/13). Informed consent was obtained from all patients diagnosed with PA and willing to participate in the clinical trial.

## Observations

In all, 60 patients of PA could be enrolled during the study period; 20 in each group. The age, body weight, sex, smoking status, alcohol intake, symptoms, KOH mount, fungal culture, type of disease and Anti-Asp-Ab titer distribution of these patients are shown in Table 1 ($P > 0.5$).

The therapeutic response and adverse reactions at two months are shown in Table 2. The radiological response was significantly inferior in group I patients as compared to the rest ($P < 0.05$). The five patients with poor clinicoradiological response belonged to this group. On the contrary, a higher number of patients in group II suffered from adverse reactions, such as, nausea, vomiting, anorexia and/or abdominal pain ($P < 0.003$) and the three patients with uncontrolled adverse reactions belonged to this group.

A within-group analysis further revealed that:

- In group I, partial radiological response was evident in all the four patients weighing <40 Kg and in four of the nine patients weighing 40 – 50 Kg, but in none of the nine patients weighing >50 Kg ($P < 0.003$).
- All the five patients in group I with poor clinicoradiological response weighed >50 Kg
- In group II, adverse reactions were reported by all the 11 patients weighing <50 Kg, but only in three of the nine patients weighing >50 Kg ($P < 0.005$)
- All the three patients in group II with uncontrolled adverse reactions weighed <40 Kg.

**Table 1: Basic parameters of the patients in three groups**

| Parameters | Group 1 | Group 2 | Group 3 | *P* |
|---|---|---|---|---|
| Mean age in years (±SD) | 42.5±8.9 | 43.8±10.7 | 44.7±9.9 | 0.795 |
| Sex | | | | |
| Male | 14 | 16 | 16 | 0.693 |
| Female | 06 | 04 | 04 | |
| Mean weight in kg (±SD) | 47.4±6.5 | 49.2±6.9 | 49.2±6.9 | 0.639 |
| Smoker | | | | |
| Current or ex | 09 | 11 | 11 | 0.767 |
| Non-smoker | 11 | 09 | 09 | |
| Alcohol | | | | |
| Yes | 04 | 05 | 05 | 0.865 |
| No | 16 | 15 | 15 | |
| Symptoms* | | | | |
| Hemoptysis | 19 | 19 | 19 | - |
| Cough | 19 | 20 | 20 | |
| Shortness of breath | 11 | 06 | 06 | |
| Expectoration | 04 | 02 | 02 | |
| Fever | 04 | 01 | 01 | |
| KOH mount | | | | |
| Positive | 08 | 07 | 07 | 0.995 |
| Negative | 06 | 07 | 07 | |
| No sputum | 06 | 06 | 06 | |
| Fungal culture | | | | |
| Positive | 12 | 13 | 15 | 0.591 |
| Negative | 08 | 07 | 05 | |
| Anti-Asp-Ab | | | | |
| <150 | 05 | 05 | 05 | - |
| >150 | 15 | 15 | 15 | |
| Type of PA | | | | |
| Early | 06 | 05 | 04 | 0.964 |
| Simple | 09 | 09 | 10 | |
| Complex | 05 | 06 | 06 | |

SD: Standard deviation, PA: Pulmonary aspergilloma

**Table 2: Therapeutic response and adverse reactions at two months**

| Parameter | Group 1 | Group 2 | Group 3 | *P* |
|---|---|---|---|---|
| Fall in Anti-Asp-Ab (%) | | | | |
| <50 | 12 | 13 | 12 | 0.932 |
| >50 | 08 | 07 | 08 | |
| Clinical response | | | | |
| Good | 10 | 12 | 15 | 0.473 |
| Partial | 05 | 05 | 05 | |
| Poor | 05 | 03 | 00 | |
| Radiological response | | | | |
| Partial | 08 | 15 | 14 | 0.048 |
| Poor | 12 | 05 | 06 | |
| Adverse reactions | 04 | 14 | 06 | 0.003 |

The therapeutic responses at six and twelve months, after the exclusion of the eight patients requiring a change in the dose of itraconazole, at two months, are shown in Table 3 ($P > 0.05$).

Tables 4 and 5 show the correlation between the therapeutic response and the type of disease. At two months, the clinical as well as radiological responses were significantly inferior in simple PA, as compared to the rest. Thereafter, the clinical response was similar in different types of PA, but the radiological response continued to be inferior in simple PA, more so at six months than at twelve months. The latter was confirmed on multivariate analysis also ($P < 0.05$).

**Table 3: Clinical and radiological responses at six and twelve months**

| At | Parameter | Group 1 | Group 2 | Group 3 | *P* |
|---|---|---|---|---|---|
| Six months (*n*=52) | Clinical response | | | | |
| | Good | 15 | 16 | 20 | 0.615 |
| | Poor | 00 | 01 | 00 | |
| | Radiological response | | | | |
| | Good | 07 | 07 | 07 | 0.699 |
| | Partial | 08 | 08 | 10 | |
| | Poor | 00 | 02 | 03 | |
| Twelve months (*n*=49)* | Clinical response | | | | |
| | Good | 13 | 15 | 18 | 0.578 |
| | Poor | 01 | 01 | 01 | |
| | Radiological response | | | | |
| | Good | 12 | 12 | 12 | 0.739 |
| | Partial | 02 | 04 | 07 | |

*One patient in each group was lost to follow-up

**Table 4: Correlation of clinical response at various time intervals with type of PA**

| Time interval | Type of PA | Good | Partial | Poor | *P* |
|---|---|---|---|---|---|
| Two months (*n*=60) | Early | 12 | 03 | 00 | 0.000 |
| | Simple | 08 | 11 | 09 | |
| | Complex | 14 | 03 | 00 | |
| Six months (*n*=60) | Early | 13 | 01 | 00 | 0.645 |
| | Simple | 23 | 06 | 00 | |
| | Complex | 15 | 02 | 00 | |
| Twelve months (*n*=56)* | Early | 13 | 00 | 01 | 0.580 |
| | Simple | 23 | 02 | 01 | |
| | Complex | 16 | 00 | 00 | |

*Four patients were lost to follow-up, PA: Pulmonary aspergilloma

**Table 5: Correlation of radiological response at various time intervals with type of PA**

| Time interval | Type of PA | Good | Partial | Poor | *P* |
|---|---|---|---|---|---|
| Two months (*n*=60) | Early | 00 | 11 | 06 | 0.000 |
| | Simple | 00 | 12 | 21 | |
| | Complex | 03 | 14 | 01 | |
| Six months (*n*=60) | Early | 08 | 05 | 02 | 0.000 |
| | Simple | 02 | 19 | 08 | |
| | Complex | 11 | 05 | 00 | |
| Twelve months (*n*=56)* | Early | 12 | 01 | 01 | 0.009 |
| | Simple | 11 | 10 | 05 | |
| | Complex | 14 | 02 | 00 | |

*Four patients were lost to follow-up, PA: Pulmonary aspergilloma

No death was recorded in the study, but three patients each in group I and II and two patients in group III had to undergo BAE during the study period. The study patients, who have now completed 12 months of therapy, are being monitored to check for relapses, if any.

## DISCUSSION

The distribution of the patients in the three groups was randomized, yet there were no differences in the three groups of this study with regard to the basic parameters ($P > 0.5$). Hence, the study data are valid for statistical comparison.

It is clearly evident from this study that the clinical as well as the radiological responses were inferior in patients on

the lower dose schedule, as compared to the variable and higher dose schedules at two months. Although, thereafter, the clinicoradiological responses were similar in the in the three groups ($P > 0.4$), this could be due to the fact that the non-responders on the lower dose schedule (group I) were excluded from the subsequent group analysis. A search of the literature failed to reveal a study that compared the efficacy of various dose schedules of itraconazole in PA. In an earlier study, Gupta *et al*.[9] have used the lower dose schedule in their patients with partial success, but Agarwal *et al*.[12] have used a dose of 400 mg of the drug in their patients, with a significantly higher success in the test group.

It was also observed in this study that a significantly higher number of patients on the higher dose schedule of the drug suffered from adverse reactions, as compared to the rest ($p \leq 0.003$), so much so, the dose of itraconazole had to be decreased in three of these patients. The frequency of adverse reactions was low, but comparable, in patients on variable and lower dose schedules. Agarwal *et al*.[12] have reported that about half of their patients on the higher dose schedule of itraconazole (400 mg/day) suffered from adverse reactions, but tolerance was not an issue in the study by Gupta *et al*.,[9] where a lower dose schedule of itraconazole (200 mg/day) was used.

A within-group analysis of patients was also consistent with the fact that the response and adverse reactions to itraconazole were dependent on the dose of the drug vis-a-vis the body weight.

Furthermore, in this study, the radiological response (and to some extent, the clinical response also) was significantly poor in patients with simple PA, as compared to the early and complex PA. Agarwal *et al*.[12] and Denning[13] observed a favorable therapeutic response to systemically administered itraconazole in their patients with chronic cavitary pulmonary aspergillosis (multiple cavitations with or without ball-like lesions). Furthermore, a six-month therapy was inadequate, as these patients continued to respond beyond this period more so, the patients with simple PA. No study has specifically correlated the sequential response to therapy in different forms of the disease.

From the above, it can be safely concluded that a weight-based variable dose schedule of itraconazole is both an effective as well as a safe modality in the management of PA, as compared to the fixed dose schedules, and therapy should be extended beyond six months, more particularly in patients with simple PA. Moreover, surgical options should be kept open for patients with simple PA, who fail to respond to the drug.

The limitations of the current study include a fewer number of patients and an inability to monitor the drug levels. Larger studies with monitoring of drug levels are required, to substantiate the above results and make substantial recommendations on the issue.

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