Editorial

Itraconazole in chronic pulmonary aspergillosis: In whom, for how long, and at what dose?

Aspergillus fumigatus, an ubiquitous fungus, can cause a spectrum of pulmonary syndromes depending on the host immune responses and the structural integrity of the airways (and the lung parenchyma).[1,2] The pulmonary disorders caused by *A. fumigatus* can be broadly classified as allergic, saprophytic or invasive, with the clinical presentation being either acute or chronic.[3] The chronic forms of pulmonary aspergillosis are largely under-recognized in the developing world, not only because of the dominant presence of tuberculosis, but also due to the lack of awareness and the paucity of investigations for routine diagnosis. *A. fumigatus* commonly complicates the course of patients with treated pulmonary tuberculosis, manifesting either with allergic sensitization or as chronic invasive disease.[4] Most cases of chronic and allergic aspergillosis are misdiagnosed and treated as tuberculosis.[5] In fact, there is a significant burden of chronic pulmonary aspergillosis (CPA) in India. In recent times, we have estimated the five-year prevalence of CPA to be about 290,147 cases in a five-year population prevalence rate of 24 per 100,000.[6]

Unfortunately, there is no consensus on the nomenclature/classification and treatment recommendations for CPA.[1,2,7,8] The use of several terms, such as, 'simple aspergilloma (SA)', 'complex aspergilloma', 'chronic cavitary pulmonary aspergillosis', 'chronic fibrosing pulmonary aspergillosis', 'chronic necrotizing pulmonary aspergillosis', 'chronic progressive pulmonary aspergillosis', 'subacute invasive pulmonary aspergillosis', 'semi-invasive pulmonary aspergillosis', 'slowly progressive chronic necrotizing pulmonary aspergillosis (CNPA),' and 'chronic pulmonary aspergillosis' only adds to the confusion.[1,9,10] Chronic forms of pulmonary aspergillosis are best conceptualized as a spectrum of diseases ranging from SA at one end to CNPA at the other [Table 1].

Simple aspergilloma is a saprophytic colonization of pre-existing cavities of *A. fumigatus*. Patients usually present with hemoptysis, but may be asymptomatic. There is no evidence of parenchymal invasion and radiologically it manifests as a single fungal ball in a thin-walled (inactive) cavity. CNPA is a semi-invasive form of pulmonary aspergillosis, which occurs in patients with mild forms of immunodeficiency (diabetes, malnutrition, steroid use) or structural lung diseases (COPD, post-tubercular sequelae). It presents as a subacute debilitating respiratory illness progressing over one to three months. The radiological features include cavities with pericavitary infiltrates and slow expansion and formation of new cavities, with or without fungal balls. Several experts identify another indolent form of chronic aspergillosis, namely, complex aspergilloma or chronic cavitary pulmonary aspergillosis (CCPA).[10] CCPA also presents with non-specific respiratory and constitutional symptoms, but has a presentation more indolent than CNPA (over months to years). The radiological manifestations include the presence of slowly expanding cavities with surrounding fibrosis (or rarely consolidation), with or without the presence of one or more fungal balls. In contrast to CNPA, there is little or no invasion of the surrounding lung parenchyma. Many authors do not differentiate between CCPA and CNPA and christen them together as CPA. However, we feel that a differentiation between the two is essential because of the different treatment implications.

Although surgery is considered the treatment of choice for SA, surgical resection may not be feasible in several patients because of medical (poor lung function, bilateral disease, underlying comorbidities) or logistical (financial constraints, lack of an experienced thoracic surgeon or patient unwillingness) reasons. This is especially true for patients with CCPA and CNPA. Also, the postoperative morbidity and recurrence rates are higher in patients with CCPA/CNPA compared to SA.[11] Hence, there is a need for nonsurgical alternatives in these patients. Several antifungal agents, both intravenous (amphotericin, micafungin, voriconazole) and oral (voriconazole, itraconazole, posaconazole) have been tried, with good success rates, in patients with CPA.[8] In fact, antifungal therapy is the cornerstone in CCPA and CNPA, with surgery reserved for those not responding to medical management. In CNPA, the aim is to treat the invasion by a fungal organism and initial therapy is generally intravenous; whereas, in CCPA, treatment with oral antifungal agents is preferred. Itraconazole, an oral antifungal agent is ideally suited for long-term therapy in these patients because of its better tolerability and lesser cost.

In the current issue of the journal, Gupta *et al.* present the results of a randomized trial on the role of itraconazole in treating patients with pulmonary aspergillomas (PA).[12]

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The authors classified aspergillomas into three groups, namely early PA, simple PA, and complex PA, and randomized 60 patients to three arms, with varying doses of itraconazole (low dose: 200 mg/day, high dose: 400 mg/day, and a weight-based dosing regimen). In contrast to the earlier studies in which the drug was given for six months, the authors treated their patients for 12 months. The major limitation of this study was the limited sample size (n = 60). Also, the use of the term 'early PA' for patients with recent thickening of cavitary walls or pleura was confusing. Cavity with pericavitary infiltrates/thickening of the wall was in fact a feature suggestive of invasion and these patients were best classified as CCPA or CNPA, depending on the rapidity of progression. As a matter of fact, the results of the provided multivariate analysis also showed that patients with early PA and complex PA had similar clinical and radiological responses.

The results of this study highlight several important facts, the main being that the medical management of CPA with itraconazole is both effective and feasible. Good clinical and radiological responses were seen in 93.8 and 73.4% of the patients, at the end of 12 months. Although the response rates are higher when compared to the earlier studies [Table 2], the duration of treatment is also longer (12 months). A possibility of interpreter bias cannot be excluded, as the study was non-blinded and the radiological assessment was only subjective.

Second, the authors proposed the concept of weight-based dosing regimen for itraconazole therapy. The authors demonstrated that the clinical and radiological response at two months was poor in the low-dose arm, with only eight of the 20 patients showing any response. All the patients who had a poor response in this arm weighed more than 40 kg, and the dose had to be escalated in five patients. None of the patients in the weight-based dosing arm needed dose modification either for poor response or for intolerance. However, we currently do not advocate the weight-based dosing

Table 1: Clinical syndromes of chronic pulmonary aspergillosis

	Simple aspergilloma	Chronic cavitary pulmonary aspergillosis	Chronic necrotizing pulmonary aspergillosis (CNPA)
Alternative names	Aspergilloma	Complex aspergilloma, slowly progressive CNPA	Subacute invasive pulmonary aspergillosis, semi-invasive pulmonary aspergillosis
Nature of *Aspergillus* infection	Saprophytic	Slow invasion	Invasive
Predisposing factors			
Systemic	None	None	Milder forms of immune deficiency Old age and malnutrition Alcoholism Diabetes Steroids
Local	Cavitary lung disease	Cavitary and structural lung diseases	Structural lung diseases COPD Pneumoconiosis Fibrocavitary diseases
Presence of an underlying cavitary lung disease	Must be present	Not necessary, but may be present	Not necessary, but may be present
Clinical progression	Non-progressive	Slow progression (>3 months)	Faster progression (1-3 months)
Evidence of pulmonary parenchymal invasion	Never present	May or may not be present	Always present
Radiological features	One or two fungal balls in the pre-existing cavity	Slowly expanding cavities/cavity with pericavitary infiltrate One or more fungal balls and pleural fibrosis may be present	Slowly expanding cavities/cavity with pericavitary infiltrate/new formation of cavities One or more fungal balls may be present
Treatment			
Surgery	Treatment of choice	May be considered if resectable and medically operable	May be considered if resectable and medically operable
Antifungal agents	Less effective (only 50% response)	Better response rates (Up to 70-75% response)	Treatment of choice

CNPA: Chronic necrotizing pulmonary aspergillosis, COPD: Chronic obstructive pulmonary disease

Table 2: Studies assessing the role of itraconazole monotherapy in patients with SA and CCPA

Author, year	Type of study	Dose used (mg/day)	Duration of treatment	Overall response rate, n/N (%)
De Beule *et al.*,[15] 1988	Retrospective observational	50-400	Variable (11-780 days)	23/42 (54.7)
Dupont *et al.*,[16]1990	Retrospective observational	200-400	Seven months	10/14 (71.4)
Tsubura *et al.*,[21] 1997	Prospective observational	100-200	NA	26/41 (63.4)
Denning *et al.*,[10] 2003	Prospective observational	400	Variable	12/17 (70.6)
Gupta *et al.*,[22] 2005	Prospective observational	200	Six months	22/33 (66.7)
Tomioka *et al.*,[23] 2011	Prospective observational	400	Three months	2/5 (40)
Agarwal *et al.*,[9] 2013	RCT	400	Six months	13/17 (76.5)

CCPA: Chronic cavitary pulmonary aspergillosis, RCT: Randomized controlled trial, SA: Simple aspergilloma

schedule, as suggested in this study. Any weight-based dosing regimen should be used only with therapeutic drug level monitoring (TDM), to titrate the drug dosage. This is because several factors other than the body weight account for the pharmacokinetic variability of itraconazole: Type of preparation (capsule vs. oral suspension), genetic polymorphisms, differences in oral bioavailability, drug–drug interactions, and the comorbidities (renal and hepatic dysfunction). It has been shown that subtherapeutic drug levels (<0.5 – 1 μg/ml) not only cause treatment failure, but also increase the risk of acquired drug-resistance in *A. fumigatus*.[13,14] We acknowledge that TDM is not routinely available in India. Hence, larger cohort studies using TDM are required, from different centers, before such weight-based regimens are used in routine care.

The study shows that long-term administration of itraconazole is safe. Of the 60 patients, adverse events were noted in 24 patients and the drug dose had to be reduced in only three patients. The study also highlights the fact that the rates of clinicoradiological response differed among various forms of CPA. The clinical (88.4 vs. 96.6%) and radiological responses (42.6 vs. 86.6%) were lower in patients with SA, as compared to others. This is logical as SA is a saprophytic colonization, whereas, CCPA is considered to be a slow, invasive disease. Earlier studies have also shown that the response rates are higher in CNPA (60–90%) as compared to CCPA (50–70%).[15,16] Thus, as a spectrum, the invasiveness of the disease as well as response rate to antifungal agents increases as we proceed from SA to CNPA.

Another concern when using itraconazole, not addressed in the current study, is the increasing rate of antifungal resistance in the isolates of *A. fumigatus*. The incidence of azole resistance among *Aspergillus* strains is on the rise in several parts of the world with the incidence rates ranging from 2 – 20%.[17] Although most data is from the western world, azole resistance in *Aspergillus* has also been reported from India.[18] Development of acquired resistance with long-term itraconazole therapy has also been reported, which is associated with treatment failure.[14,19] More studies are needed to determine the incidence of primary and acquired resistance to *A. fumigatus* isolates in India.

The optimal duration of therapy for CPA needs to be determined. Some recommend lifelong therapy although this is not always practical. The current study suggests that continuing therapy beyond six months improves the radiological response rate (40.4 vs. 73.5%), but not the clinical response rate (98.1 vs. 93.9%). Patients with chronic forms of aspergillosis have high relapse rates of up to 50% following cessation of antifungal agents.[9,20] Whether prolonged therapy decreases the risk of future relapses needs to be addressed. It is of paramount importance that future studies identify factors predicting a relapse, as it may help in the selection of a subgroup of patients who require a longer duration of therapy.

In conclusion, CPA is an under-recognized entity in India. *Aspergillus*-related disorders should be routinely considered in those presenting with cavitary lung disease, especially in those who are sputum smear–negative for acid-fast bacilli, instead of a routine introduction of the empirical anti-tuberculosis therapy.

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