



## CASE REPORT

# The efficacy and tolerability of voriconazole in the treatment of chronic cavitary pulmonary aspergillosis

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### KEYWORDS

Fumigatus;  
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Complication

**Summary** Voriconazole is the second oral drug licensed for the treatment of aspergillosis. A retrospective non-comparative study was conducted in 16 patients with chronic cavitary pulmonary aspergillosis (CCPA) treated with voriconazole. All patients had failed or were intolerant of itraconazole. The duration of therapy varied from 3 days to 16.5 months. Eleven patients received at least 3 months of therapy with no significant adverse events. Overall seven (64%) patients had a response at 3 months as assessed by at least some fall in inflammatory markers, weight gain and reduction in pulmonary symptoms and two (18%) remained stable. Inflammatory markers improved in 5/11 (46%) with a mean fall in CRP of 0.08 mg/l and ESR of 12.8 mm/h. *Aspergillus* precipitins were quantitated by numbers of arcs and serum dilution and 11 (100%) showed improvement of at least one band or fall of titre. Total serum IgE was elevated (> 200 IU/mL) in 5/11, and fell by a median of 118 kIU/l. Two patients failed therapy. Of the 17 patients, five (27%) had to discontinue therapy as a result of adverse events (three in under 1 week). Adverse events included erythematous rash (5), headaches (4), hepatotoxicity (3), photosensitive rash (3), retinal flashes (3) and neurological symptoms (3). Voriconazole is a useful alternative therapy for CCPA, with a response rate of 64%, over 3 months, and continuing partial remission of disease for much longer periods.

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The chronic forms of pulmonary aspergillosis have not always been clearly delineated because the prior conceptual framework was inadequate to explain all the clinical manifestations seen. Chronic

cavitary pulmonary aspergillosis (CCPA) is a newly categorized entity characterized by slowly progressive and symptomatic disease with multiple pulmonary cavities, with or without pleural thickening, with or without one or more aspergillomas (or fungus balls), positive *Aspergillus* precipitins and raised inflammatory markers.<sup>1</sup> These patients require antifungal therapy to improve symptoms and to prevent the development of pulmonary fibrosis.

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For patients with CCPA, oral antifungal therapy is preferable to intravenous therapy given the chronicity of the disease. Itraconazole has had mixed results, with criteria for response governing the perception of efficacy. In 17 patients also managed by the senior author, 12 (71%) improved or stabilised. Others have shown mixed results. Only marginal benefit was found in one study, but the study group included those with simple aspergillomas, and the itraconazole dose was only 200 mg daily.<sup>2</sup> Another study concluded that itraconazole was an effective alternative to the relatively toxic intravenous amphotericin B.<sup>3</sup> A Japanese study confirmed that itraconazole penetrates aspergillomas, by showing detectable concentrations in surgically removed fungal balls.<sup>4</sup> In such a chronic disease intravenous therapy has a limited place, but is useful when oral therapy fails or is toxic. Amphotericin B yielded short-lived responses in 9 of 11 (82%) patients.<sup>1</sup> There are no published data on the utility of caspofungin in this setting. Surgical resection is fraught with complications for patients with CCPA, as demonstrated by the poor results in patients with 'complex' or 'complicated' aspergillomas'.<sup>1,5,6</sup> In cases where haemoptysis is a problem, embolisation of bronchial vessels may lead to some symptomatic relief.<sup>7</sup>

In view of these management challenges, we conducted a retrospective, open, non-comparative study in patients with CPA treated with voriconazole to assess its efficacy and tolerability.

## Materials and methods

Patients included all those referred to the senior author (DWD) up until January 2004 with the following criteria:<sup>1</sup> Chronic pulmonary or systemic symptoms (>3 months) including at least one of weight loss, productive cough or haemoptysis, and cavitory pulmonary lesion with evidence of paracavitary infiltrates or expansion of cavity size over time, and positive serum *Aspergillus* precipitins test, and elevated inflammatory markers, and exclusion of other pulmonary pathogens by appropriate cultures and serology that are associated with a similar disease presentation and no overt immunocompromising conditions.

Patients attended outpatient clinics at regular intervals while on therapy, soon after starting therapy and then monthly or 2 monthly in most instances. Cough, sputum production, sputum volume, chest pain, haemoptysis, shortness of breath and general well being were all assessed using severity scales of 1=none, 2=mild,

3=moderate, 4=severe for most symptoms. A scale of 1-6 was used for shortness of breath, and 1-5 for haemoptysis and general well-being. Weight was measured at each visit. Laboratory levels of inflammatory markers were obtained as were levels of serum *Aspergillus* precipitins and titres (Microgen Bioproduct) and IgE levels (Immunocap, Pharmacia) in order to assess response.

Data was collected at intervals of 1, 2, 3, and 6 months with 3 months being the minimum time on therapy required for assessment of efficacy. After 6 months the patient was next evaluated at 1 year. Radiological change was not formally assessed in this short time frame, but was used to determine failure if significant deterioration (usually new cavity formation) was observed. Patient responses were categorized as improved, stable or failed. Failure was the outcome if there was no improvement in a patient's clinical, serological or radiological findings.

All adverse events recorded in the notes at outpatient clinic attendances were noted and the likelihood of a relationship to the voriconazole therapy determined. An adverse event was any, which, in the opinion of the physician, was possibly or probably related to voriconazole treatment. Dose reduction was required in cases where patients were unable to tolerate a particular dose of voriconazole. Often if the severity of side effects were mild the patient continued without changes to dosages. If the side effects were deemed serious or especially adverse then the dose of voriconazole was often reduced. If voriconazole continued to be poorly tolerated despite dose reduction then treatment was discontinued. Therapy was discontinued if reactions were severe, in the case of abnormal liver function tests the drug was discontinued if levels were abnormal.

Concentrations of serum voriconazole were also regularly monitored using an LCMS assay recently described.<sup>8</sup>

## Results

We identified 16 patients with CCPA who had received voriconazole. All were intolerant or failing itraconazole. Most had received multiple prior therapies, some for many years. They were commenced on 150-200 mg twice daily of voriconazole, with dose adjustment dependent on plasma monitoring and tolerance. The duration of therapy varied from a few days to >18 months. Eleven patients received at least 3 months voriconazole therapy.

**Table 1** Objective parameters of response at 1 and 3 months (n=11)

Parameter (n)	Baseline value (mean+SD)	1 month change (mean+SD)	No (%) improved at 3 months	Mean change over 3 months
Weight (kg) (11)	57.8	-1.3	4/10 (40)	0.1
ESR (mm/h) (11)	49.5	-0.04	8/9 (89)	-12.8
CRP (mg/l) (11)	48.5	0.07	8/11 (73)	-0.08
Total IgE (8)	645.3	-8.8	4/5 (80)	-119
<i>Aspergillus</i> precipitins (titre) (reciprocal serum dilution) (7)	18.1	-0.2	7/7 (100)	-1.0
<i>Aspergillus</i> precipitins (arcs) (8)	3.8	-0.4	4/6 (67)	-2.4

Number in brackets, number of patients with test results for that test type.

Assessment of symptoms showed a variable response. At 3 months 3/11 (27%) had improvement in cough, 6/11 (55%) in sputum production and 5/11 (46%) sputum volume, while 4/10 (40%) showed improvement in chest pain, 4/11 (36%) in shortness of breath, and 6/11 (55%) in general well-being. Weight gain was marginal, 4 of 10 in whom it was recorded gained weight, a mean overall of 0.1 Kg (Table 1).

Inflammatory markers improved in 5/11 (46%) with a mean fall in ESR of 12.8 mm/h and fall in CRP of 0.1 mg/l (Table 1). *Aspergillus* precipitins were quantitated by numbers of arcs and serum dilution and 100% showed improvement of at least one band or fall of titre (Table 1). Total serum IgE was elevated (>200 IU/mL) in 5/11, and fell by a median of 118 kIU/l (Table 1).

Overall seven (64%) patients had a response as assessed by at least some fall in inflammatory markers, weight gain and reduction in pulmonary symptoms and 2 (18%) remained stable. Two patients failed therapy.

At 18 months one patient grew an isolate of *A. fumigatus* newly resistant to voriconazole. He clinically failed therapy and required alternative therapy.

Voriconazole was generally well tolerated with the majority of patients experiencing what were deemed as minor side effects. In the study five patients experienced symptoms that required cessation of therapy, these were mainly due to abnormal liver function tests, retinal flashes and neurological symptoms such as paraesthesiae. An erythematous photosensitive rash was the most prevalent side effect but this was generally tolerated by most patients with avoidance and precautions taken with regards to sunlight.

### Case history

A 58-year-old social worker had a long history of pulmonary disease. During her late teens she had

had two simple pneumothoraces leading to an open pleurodesis. She remained well with several small simple cysts at the apex of the right lung. She was diagnosed with aspergillosis in 1993 after developing a constant cough, weight loss and increasing fatigue. She had strongly positive *Aspergillus* precipitins and growth of *A. fumigatus* from bronchoalveolar lavage fluid and sputum on several occasions. In 1999 a CT scan showed both lungs to be hyperinflated and a right upper lobe cavity (9.2 cm<sup>2</sup>) with a thick irregular wall and a small amount of debris within it. The adjacent lung was collapsed and bronchiectatic. A CT guided lung biopsy was performed and the lung tissue showed chronic inflammatory reaction without hyphae being visualised. She failed therapy with itraconazole but responded to 12 weeks of intravenous amphotericin B. Subsequently poor health was minimized with itraconazole and gamma interferon 20 ug subcutaneously three times weekly for 3 years. However, following worsening of symptoms and deterioration radiologically she was commenced on voriconazole therapy (150 mg twice daily) in December 2002. Her ESR was 24 mm/h and precipitin and titre levels both strongly positive. She noticed improvement in symptoms after 2 months of treatment but complained of tiredness associated with voriconazole. Her ESR had dropped to 19 mm/h and but *Aspergillus* precipitins remained strongly positive. At this point her voriconazole plasma concentration was 0.46 mg/l post dose. Due to the side effect of tiredness, her dose was decreased to 100 mg twice daily. Two months after reduction in dose, post dose voriconazole levels dropped to 0.28 mg/l. At 8 months of therapy she had made definite improvement, commenting on increased levels of energy and a decrease in symptoms. She had also gained weight. The only side effect experienced at this point being a mild generalized pruritis, similar to that which she has experienced while taking itraconazole

previously. After 18 months of voriconazole treatment she continues to be reasonably well.

## Discussion

Voriconazole is active against all common *Aspergillus* species in vitro,<sup>9</sup> and is superior to amphotericin B in invasive aspergillosis.<sup>10</sup> Although an azole, it differs in structure from itraconazole and has different pharmacokinetics, an extended spectrum of activity against rarer fungal pathogens, a slightly different drug interaction profile and a different adverse event profile.<sup>11</sup> Like itraconazole, but for different reasons, it exhibits wide inter-patient variation in exposure after both intravenous and oral dosing.<sup>11,12</sup>

Recently chronic pulmonary aspergillosis has been reclassified to separate simple aspergilloma (which may remit and have few associated symptoms) from what was called complex or complicated aspergillomas by some thoracic surgeons. We renamed this entity CCPA to emphasise the distinction with simple aspergilloma, its chronicity and its radiological hallmark of multiple slowly evolving cavities often not containing an aspergilloma.<sup>1</sup> Both these entities need to be distinguished from chronic necrotising pulmonary aspergillosis (CNPA) which in its most aggressive form is invasive, albeit slowly (hence the alternative term sub-acute invasive pulmonary aspergillosis (IPA)).<sup>1</sup> In fact prior publications describing CNPA have included some patients with subacute IPA and others with CCPA making it difficult to compare response rates. In reality, there is most probably a continuum from IPA to the simple aspergilloma.<sup>13</sup>

A key pathological distinction between subacute IPA and CCPA is the presence of *Aspergillus* hyphae in tissue in the former, as opposed to within cavities. Patients with subacute IPA are often slightly immunocompromised, more acutely ill and may have fever.<sup>14,15</sup> Biopsies of lesions or percutaneous aspiration of lesions is usually productive in subacute IPA (culture or histology) but not in CCPA, reflecting the larger burden of organisms in subacute IPA and more rapid tissue destruction. In both cases, new cavities in the lung are formed, cavities enlarge, sputum or BAL fluid may contain *Aspergillus* spp., inflammatory markers are raised and *Aspergillus* precipitins are detectable in blood. What distinguishes them most is the pace of the disease, which usually reflects any underlying disease. Patients with CCPA are non-immunocompromised but typically have prior pulmonary disease (especially atypical mycobacterial infection or sarcoidosis), are often deficient in mannose binding protein,<sup>16</sup> whereas those with subacute IPA

usually have an some immunodeficiency state such as diabetes mellitus, HIV infection or are in receipt of corticosteroids. The pace of radiological progression in subacute IPA is measured in weeks or months and is obvious, whereas in CCPA it is measured in months or years and is subtle. Patients with CCPA most commonly present with a chronic productive cough and weight loss. Both these groups of patients differ from those with simple aspergillomas who have single well-contained fungal balls in solitary pre-existing cavities, or enlarged bronchi, usually with trivial symptoms.

Untreated CCPA leads to untrammelled pulmonary fibrosis (described as chronic fibrosing pulmonary aspergillosis<sup>1</sup>). Successful treatment with itraconazole has been reported in a number of studies.<sup>17,18</sup> Advantages of this treatment include oral administration, a relatively benign side effect profile and a long-term safety record.<sup>19</sup> Cessation of itraconazole therapy is mostly a result of development of adverse events or deterioration of clinical status which may be associated with antifungal resistance in vitro.

Surgical therapy (lobectomy, cavernostomy or pneumonectomy) may be considered in persons unable to tolerate chemotherapy. These procedures are still in use today but there is a large morbidity and some mortality associated with surgery in CCPA as the patient often already has a severely compromised respiratory system, is typically cachectic, and technical challenges accompany these operations. Courses of intravenous amphotericin B and/or embolisation for haemoptysis are preferable, if possible.

In patients unable to take itraconazole, voriconazole is the only viable alternative for outpatient therapy. Our experience indicates that voriconazole was 62% effective in those able to take treatment for 3 months or longer, and 44% effective overall. Responses were rarely complete in most patients. Although not assessed formally, radiographic change was limited, and from experience it takes years to achieve the optimal outcome of thin walled cavities, with limited pleural thickening. As voriconazole is newly available, it is expensive and long term experience limited. Of concern is the development of voriconazole resistance after many months of therapy. However for many patients it carries very significant benefits.

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