


Pulsed echinocandin therapy in azole intolerant or multiresistant chronic pulmonary aspergillosis: A retrospective review at a UK tertiary centre

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Abstract

Introduction: Chronic pulmonary aspergillosis (CPA) is a fungal disease with high mortality and morbidity. Guidelines suggest treatment with azoles as first-line therapy. However, patients often develop treatment intolerance or increasingly azole resistance.

Objectives: This retrospective review assesses outcomes in azole resistant or intolerant patients with CPA treated with cyclical echinocandin therapy.

Methods: We retrospectively examined records of 25 patients with CPA treated with cyclical caspofungin, 6 of whom were either azole-resistant or azole intolerant. Baseline characteristics, high-resolution computed tomography severity scores, forced expiratory volume after 1 minute (FEV1), forced vital capacity (FVC), body mass index and serology (*Aspergillus fumigatus*-specific IgG, *Aspergillus fumigatus*-specific IgE, total IgE and CRP) were assessed before and after caspofungin.

Results: Of the six patients, four (66%) started caspofungin due to intolerance and two (33%) due to pan-azole resistance. On treatment, there was stability in FEV1 with an overall mortality of 33% during the follow-up period with a median survival of 875.5 days (IQR 529-1024). No significant change in serology (*A. fumigatus*-specific IgG and CRP) was seen.

Conclusions: With pulsed echinocandin therapy, azole-intolerant or pan-resistant CPA patients have similar mortality rates to azole-naïve CPA patients. Pulsed echinocandin therapy may present a strategy to stabilize CPA in patients with pan resistance or intolerance to, azole therapy.

KEYWORDS

azoles, caspofungin, CPA, drug resistance, echinocandins, fungal, pulmonary aspergillosis

Abbreviations: CPA, Chronic pulmonary aspergillosis; HRCT, high-resolution computed tomography (of the chest); ABPA, allergic bronchopulmonary aspergillosis; FEV1, Forced expiratory volume over 1 minute; FVC, Forced vital capacity; BMI, Body mass index; CRP, C-reactive protein; IgE, Immunoglobulin E; Aspergillus IgG, Immunoglobulin G antibodies to *A. Fumigatus* using fluoroenzyme immunoassay (ImmunoCAP); Aspergillus IgE, Immunoglobulin E antibodies to *A. Fumigatus* using fluoroenzyme immunoassay (ImmunoCAP); COPD, Chronic obstructive pulmonary disease; MIC, Minimum inhibitory concentration; NTM, Non-tuberculous mycobacteria; IQR, Interquartile range.

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1 | INTRODUCTION

Chronic pulmonary aspergillosis (CPA) lies at the severe end of a spectrum of diseases caused by *Aspergillus spp.*¹ *Aspergillus spp.* are saprophytic fungi commonly found in soil and decaying organic material, and are thus fairly ubiquitous to most environments. Depending on the host immune response, inhalation can lead to a range of pulmonary disease manifestations, from allergic sensitization and allergic bronchopulmonary aspergillosis to acute invasive aspergillosis and CPA. Most pulmonary aspergillus disease is attributed to *Aspergillus fumigatus*, but *Aspergillus flavus* and *Aspergillus niger* may also be implicated.

CPA occurs usually, but not always, in patients with predisposing risk factors. These include structural lung damage, such as previous tuberculosis, chronic obstructive pulmonary disease or mild immunosuppression such as from diabetes mellitus or chronic steroid use.² Non-tuberculous mycobacteria (NTM) infection patients are at increased risk of CPA, but causality as opposed to an overlap of risk factors has not been established.^{2,3} More recently, polymorphisms in the innate Toll-like receptor (TLR) family, specifically TLR-4, have been associated with increased susceptibility to CPA.⁴

In contrast to invasive aspergillosis, CPA usually has an insidious onset, with symptoms developing over a period of months to years. Classical symptoms include shortness of breath, cough, haemoptysis and weight loss.¹ Diagnosis is multimodal and involves characteristic findings on high-resolution computed tomography (HRCT), direct evidence of *Aspergillus spp.* (through fungal culture or PCR from broncho-alveolar specimens) or immunological response (*Aspergillus*-specific IgG or precipitins).⁵ Mortality is high despite antifungal therapy, with reports showing a ~30% mortality at 1 year.⁶

Antifungal therapy is primarily based on oral azoles.¹ Itraconazole has been shown to be efficacious in CPA.^{7,8} Other studies have demonstrated efficacy of posaconazole and voriconazole.^{9,10} Intolerance is common, however, with a recent study showing ~30% discontinuation over a 12-month period due to adverse effects.¹¹ Of increasing concern, rates of azole resistance in *A. fumigatus* are increasing.¹² Treatment options in CPA patients with azole-resistant *Aspergillus spp.* or those who are azole intolerant are limited and data on outcomes in this challenging group is sparse. Alternatives, such as short-term courses of intravenous liposomal amphotericin B, has been associated with acute kidney injury rates of up to 32%.¹³ In our centre, caspofungin therapy has been shown to be effective in the treatment of CPA in the context of sarcoidosis, where it is used preferentially over amphotericin B due to better tolerability and reduced toxicity in this frail cohort.¹⁴ A recent study has also highlighted their tolerability as parenteral outpatient antimicrobial therapy in patients with CPA.¹⁵

Echinocandins (including caspofungin, micafungin and anidulafungin) are fungistatic to *Aspergillus sp.*, inhibiting cell wall synthesis.^{16,17} There is clear evidence for their use in invasive aspergillosis as alternatives to amphotericin B or voriconazole; however, the evidence for their use in CPA is less well established.^{5,18} Given the different mechanism of action to azoles, murine data have suggested dual therapy may potentially be additive or synergistic.^{17,19} Previous studies have shown effectiveness of micafungin in treatment of CPA but with limited follow-up duration.^{5,20,21}

In the light of these challenges described, we have retrospectively reviewed a small cohort of CPA patients with either intolerance or resistance to all azoles, who were treated with pulsed caspofungin as salvage therapy. A defined radiological scoring system for CPA, lung function, body mass index (BMI) and serological biomarkers were used to assess outcome in these patients with limited treatment options for CPA.

2 | MATERIALS AND METHODS

Electronic Patient Records at the Royal Brompton Hospital, a single tertiary referral centre, were interrogated for CPA patients treated with intravenous caspofungin between 2008 and 2012. Patients with cystic fibrosis or those who received only a single cycle were excluded. Patients were diagnosed with CPA based on a combination of clinical symptoms, radiological features, microbiological fungal culture and serology, as defined in recently published guidelines.⁵ A total of 25 patients were identified, of whom six had either pan-azole resistance (itraconazole, voriconazole and posaconazole) or were azole intolerant. In pan-azole resistance, azole therapy was continued with parenteral caspofungin therapy used as adjunctive therapy. Azoles used included itraconazole, voriconazole and posaconazole.

Azole resistance to *A. fumigatus* was interpreted based on epidemiological cut-off values (ECV). For itraconazole or voriconazole, minimal inhibitory concentration (MIC) of ≤ 1 mg/L were defined as susceptible, 2 mg/L as intermediate, > 2 mg/L as resistant; for posaconazole MIC of ≤ 0.25 mg/L as susceptible, MIC of 0.5 mg/L as intermediate and MIC of > 0.5 mg/L as resistant.²²

Caspofungin was given intravenously at a dose of either 70 mg on day 1 and 50 mg daily thereafter (> 80 kg) or 50 mg daily (≤ 80 kg) for 14 days. Cycles were planned for 8-week intervals. Intravenous antibiotics were given concomitantly with caspofungin for the cycle duration if indicated based on previous microbiology and clinical response. Patients on treatment for NTM continued anti-mycobacterial therapy for the duration. Radiology was graded by independent radiologist assessment of HRCT scans (Authors CS and DH). Each lobe was graded by cavity diameter (mm), cavity wall

thickness (mm), pleural thickness (mm), tree-in-bud signs and consolidation (%). This was performed before and after caspofungin treatment.

Patient demographics, including age and co-morbidities were recorded. BMI, C-reactive protein (CRP), total IgE, *A.fumigatus*-specific IgG, *A.fumigatus*-specific IgE and spirometry results were retrieved from electronic and case notes before and during caspofungin treatment. *A.fumigatus*-specific IgG and IgE levels were measured using ImmunoCAP fluoro-enzyme immunoassay (Phadia AB, Uppsalla, Sweden).

Outcomes for patients were categorized as improved or worse if there was a change of $\pm 5\%$ at the end of caspofungin treatment from pretreatment baseline. Survival was calculated from the start of caspofungin treatment up to death or 01/12/2015, whichever was first. Categorical variables data are expressed as frequencies or proportions. Continuous data are expressed as means with standard deviation (SD) for parametric data or medians with interquartile ranges (Q1-3) for non-parametric data. Data were analysed using SPSS Statistics (IBM SPSS Statistics for Macintosh, version 22.0, Armonk, NY, USA: IBM Corp.). As a retrospective, non-interventional project, this study has been reviewed by our local trust research board and was deemed service evaluation and hence did not require formal ethical approval.

3 | RESULTS

Six patients with azole-resistant or azole-intolerant CPA received regular pulsed intravenous caspofungin during 2008-2012. Patient demographics prior to caspofungin treatment are outlined in Table 1. Baseline data for patients were not available as these were tertiary referrals.

Mean age was 54.5 years (range 39-66). The most common fungal pathogen isolated was *A. fumigatus*, *A. niger* was isolated in one patient. Patients received between 6 and 10 cycles of caspofungin with a median gap between cycles of 64 days (IQR 51-81). Of the six patients, four (66%) started caspofungin due to intolerance and two (33%) due to pan-azole resistance. Three of the four (75%) patients with concurrent NTM disease were treated for NTM prior to or during the course of their caspofungin treatment. Baseline spirometry was available for five (83%) of patients with mean FEV1 of $41 \pm 21\%$ and forced vital capacity (FVC) of $67 \pm 28\%$; FEV1/FVC ratios showed a restrictive and obstructive pattern in two and three patients, respectively.

Individual patient outcomes are summarized in Table 2. At the end of follow up, 66% (4/6) of patients survived, with a median survival of 875.5 days (IQR 529-1024). Baseline median *A. fumigatus*-specific IgG levels, total IgE levels and CRP were 172.0 mg/L (IQR 126.0-184.0), 145.5 IU/mL (53.0-283.8) and 32.5 mg/L (IQR 18.8-64.3), respectively. At the end of caspofungin treatment median

TABLE 1 Patient demographics

| Patient | Co-morbidities | | | | Microbiology | | Treatment | | Reason for Caspofungin | No. Cycles Caspofungin | | |
|---------|----------------|-----|-------------------|------------------|----------------|---------|-------------------------|-------------------------|------------------------|---|--|---------------|
| | Age | Sex | FEV1 ^a | BMI ^a | Smoker | Sarcoid | Co-morbidities | <i>Aspergillus</i> spp. | | | NTM | Azole therapy |
| 1 | 61 | M | 24.5 | 15.4 | - ^b | No | - | <i>A. fumigatus</i> | <i>M. Fortuitum</i> | Itraconazole/Posaconazole | Intolerant (Cardiomyopathy) | 10 |
| 2 | 39 | M | 70.2 | 20.5 | - ^b | No | - | <i>A. fumigatus</i> | <i>M. Avium</i> | Itraconazole | Azole pan-resistant | 10 |
| 3 | 53 | F | 30.0 | 26.6 | Yes | Yes | Hepatitis C, heroin use | <i>A. fumigatus</i> | No | Itraconazole/Voriconazole | Azole pan-resistant | 8 |
| 4 | 66 | M | 36.8 | 19.5 | - ^b | No | Pericarditis | <i>A. niger</i> | No | Voriconazole | Intolerant (Cardiomyopathy) | 8 |
| 5 | 57 | M | - ^b | - ^b | Ex | Yes | COPD, Hypothyroidism | <i>A. fumigatus</i> | <i>M. Xenopi</i> | Itraconazole/Voriconazole | Intolerant (Hepatitis) | 10 |
| 6 | 51 | F | 64.4 | 22.1 | Never | No | - | <i>A. fumigatus</i> | <i>M. avium</i> | Itraconazole/Voriconazole/Posaconazole/ | Intolerant (Peripheral neuropathy, peripheral oedema, hair loss) | 6 |

Abbreviation: NTM, non-tuberculous mycobacteria.

^aAt baseline.

^bMissing data points.

TABLE 2 Patient outcomes

| Patient | Demographics | | | Serology | | | Radiology | | | Inflammation | | | Outcome | |
|---------|----------------|----------------|----------------|----------|------------------|-------------|-----------------------|-----------------|-------------------|--------------|------------------------|----------------------------|----------|--|
| | BMI | FEV1% | FVC% | CRP | IgG ^d | Cavity Size | Cavity Wall Thickness | % Consolidation | Pleural Thickness | Tree-in-Bud | Inflammation in Cavity | Days Survival ^c | Outcome | |
| 1 | Improved | Improved | Improved | Stable | Improved | Stable | Stable | Stable | Stable | Improved | Worse | 1765 | Survived | |
| 2 | Improved | Stable | Stable | Improved | Worse | Improved | Improved | Worse | Stable | Improved | Stable | 1052 | Survived | |
| 3 | Improved | Stable | Improved | Worse | Worse | Stable | Worse | Stable | Worse | Improved | Stable | 940 | Survived | |
| 4 | – ^a | – ^a | – ^a | Worse | Worse | Worse | Worse | Improved | Improved | Worse | Stable | 400 | Died | |
| 5 | – ^a | – ^a | – ^a | Better | Improved | Worse | Stable | Worse | Improved | Worse | Stable | 811 | Died | |
| 6 | Worse | – ^a | – ^a | Worse | Worse | Stable | Worse | – ^b | Improved | Improved | Stable | 435 | Survived | |

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FEV1, forced expiratory volume in 1 minute; FVC, forced vital capacity.

^aMissing data points.

^bNo consolidation.

^cDays survival up to 01/12/2015.

^d*A. fumigatus*-specific IgG.

levels were similar (150 mg/L (IQR 49.6–200.0), 53.0 IU/mL (IQR 7.3–216.5), 33.5 mg/L (IQR 24.8–39.3), respectively). Median changes for *A. fumigatus*-specific IgG levels are shown in Figure 1.

Quantitative analysis of HRCT images from initiation of cyclical Caspofungin therapy to follow-up census (end of study duration or death) showed a mixed response. In both patients who died in the study duration, there was a notable increase in cavity size, suggesting that this may be a useful marker of disease progression. In the other four patients, on pulsed caspofungin therapy, there was either stability or improvement in cavity size. There was a variable response in cavity wall thickness. Overall, over 6 months of pulsed caspofungin therapy, median change in cavity wall thickness was 0.0 mm (IQR –2.2 to +2.0), pleural thickness was 0.0 mm (IQR –0.5 to +0.3) and cavity size was +2.35 mm (IQR –8.0 to +13.0) and in lung consolidation was 0.0% (IQR –12.5 to +3.8).

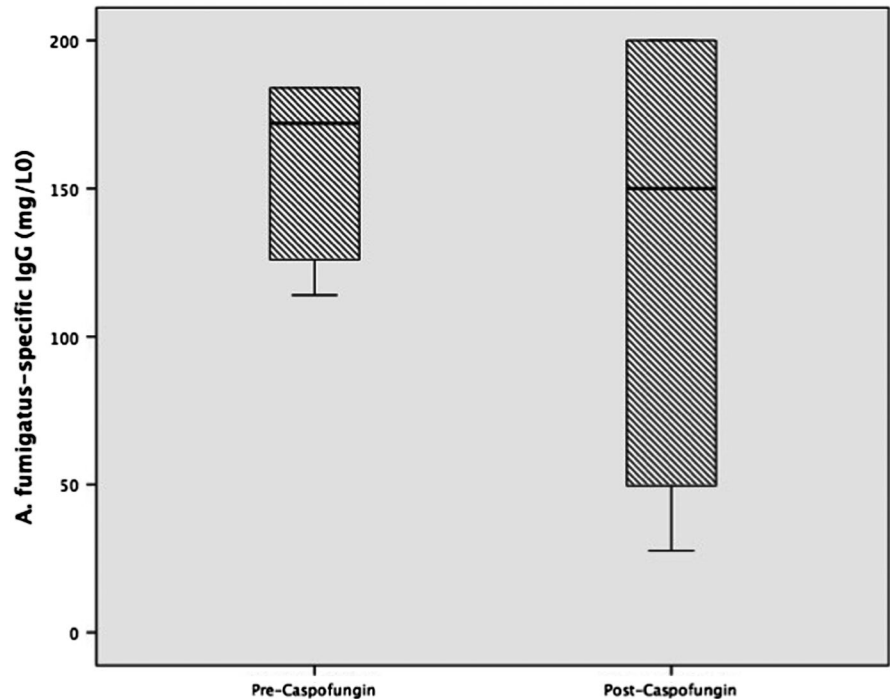
4 | DISCUSSION

With increasing rates of azole resistance amongst *Aspergillus spp.* and for those intolerant of azoles, alternative and non-toxic therapies are urgently needed. This retrospective review describes outcomes in a small cohort of azole-resistant and azole-intolerant CPA patients treated with cyclical caspofungin as salvage therapy. We show a trend towards stability in BMI, lung function and radiology in a majority of these patients with highly limited treatment options.

To date, in published case series of CPA, the majority of patients have been treated with azole therapy, which remains the mainstay of treatment. However, there is a rising incidence of azole resistance amongst *Aspergillus spp.* and an established high prevalence of azole intolerance.^{11,12} Echinocandin therapy is generally well tolerated and can be given safely as an outpatient.¹⁵ There is though, limited data on its efficacy in CPA as salvage therapy in azole intolerant of pan-resistant cases. A study of micafungin in 70 patients with deep-seated mycoses found a good response in patients with previously ineffective or toxic antifungal therapy; however, only 9 patients in the study were diagnosed with CPA, of which 6 showed response to micafungin.²¹ A multicentre trial in 2010, randomized CPA patients to voriconazole or micafungin and found no significant difference in response. This was, however, assessed only 4 weeks after treatment, with no information available on subsequent morbidity or mortality.²⁰

Baseline patient demographics of our cohort are comparable to previous published studies with a median age of 54.4 years and a median baseline BMI of 20.8 kg/m². However, two thirds of our cohort were co-infected with NTM, which is a higher proportion than previous studies.^{6,23}

FIGURE 1 Median change in *Aspergillus*-specific IgG. This boxplot represents the median change in serum *Aspergillus*-specific IgG before and after caspofungin with interquartile ranges (Q1-3)



Mortality (2/6, or 33%) is also comparable to the existing published literature with azole naïve patients.^{6,24} There was no significant improvement in serology; however, the use of serial *Aspergillus*-specific IgG to monitor treatment response has recently been questioned.²⁵

Quantitative radiology showed a mixed response during pulsed caspofungin therapy. All surviving patients showed improvement in cavity size. Within the published literature to date, the radiological response in CPA to antifungals has been mixed. Denning et al found arrest of cavity expansion to be a marker of improved clinical state, despite cavity wall thickness being an unreliable marker of disease activity.²³ In a study by Agarwal et al, a positive outcome was not defined by improvement in radiological or mycological parameters, but a prevention of deterioration.⁷ A previous review by Desai et al noted that in some series, HRCT features improve in only about half of patients.²⁶ However, a recent study quantitatively evaluating the radiological response of CPA patients to antifungal therapy revealed a significant association of reduction in cavity and pleural wall thickness with a positive clinical response.²⁷ In our study, both patients who died during the follow-up period had improvements in pleural wall thickness, however. In the same study, a change in cavity size was not associated with clinical outcome. It is hence, still unclear, what radiological markers correlate accurately with disease progression and clinical outcome.

In vitro and in vivo studies have shown azole-echinocandin synergy against *A. fumigatus* with increased synergy shown in azole-resistant strains likely due to the underlying azole resistance mechanism.²⁸ In addition, apart from inhibition of *Aspergillus spp.* growth, echinocandins

induce morphological changes in *A. fumigatus* hyphae, increase exposure of beta-glucan and subsequently increase macrophage-mediated inflammatory responses *in vitro*.²⁹ This hypothetically may induce a longer lasting immune response in the host than the echinocandin course, which only has a half-life of 9-11 hours.³⁰ This potentially suggests a role for echinocandins as salvage therapy in CPA.²⁸

As a retrospective historical analysis, this study has a number of limitations. Our cohort is small, from a number of years ago and from a single tertiary referral centre and is heterogeneous with multiple co-morbidities. We were unable to compare efficacy of caspofungin therapy to a control group, as all patients with azole-refractory CPA received caspofungin. Demographics within our cohort are, however, comparable to the published literature.⁶ However, these are “real-world” data and reflect the precarious treatment of this difficult and rare disease, with little available data regarding outcome in these patient groups. Treatment options have not changed since this dataset was collected and azole resistance globally is increasing, highlighting the importance of looking at alternative therapeutic options. As a retrospective study, we were, however, unable to collect objective patient-centric outcomes. As treatment is mainly aimed at disease stabilization, clinical symptom response is an important factor, and is associated with outcome.⁶

Nevertheless, this study demonstrates the potential benefit of cyclical caspofungin therapy for individuals with CPA with azole intolerance or resistance disease to achieve disease stabilization and highlights the need for adequately powered prospective multicentre studies to determine the most effective therapeutic option in this challenging patient group.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHORS CONTRIBUTIONS

AS, RW and ML were involved in study design and patient identification. MF, SB and EG performed all data collection. MF, WO and AS performed data analysis and wrote the original draft of the manuscript. CS and DH assessed and graded CT chest images. All authors were involved in manuscript editing.

ETHICS

This study was reviewed by our local trust research board and as a retrospective, non-interventional project, was deemed service evaluation and hence did not require formal ethical approval.

CONSENT FOR PUBLICATION

All authors have consented to the publication of the manuscript

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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