Efficacy and Safety of Posaconazole for Chronic Pulmonary Aspergillosis

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(See the editorial commentary by Kohno, on pages 1392–1394.)

Background. Chronic pulmonary aspergillosis (CPA) is a severe, progressive respiratory infection characterized by multiple pulmonary cavities and increased levels of antibodies to *Aspergillus* species. We report the first use of posaconazole in patients with CPA.

Methods. A retrospective study was performed. A composite clinical and radiological evaluation was used to assess response to posaconazole therapy. The rates of clinical response and failure after 6 and 12 months of therapy were determined. Kaplan-Meier survival models were developed to describe the time to clinical response and failure. The underlying diagnosis, the type of therapy (primary or salvage), *Aspergillus* antibody titer, and posaconazole serum concentrations were assessed as covariates. *Aspergillus* species were identified and minimum inhibitory concentrations (MICs) of triazoles were determined using standard techniques.

Results. There were 79 patients that initially received posaconazole 400 mg twice per day. The median age of patients was 61 years, and 57% were male. Response to posaconazole was observed in 61% of patients at 6 months and in 46% at 12 months. Kaplan-Meier plots showed that the first response to posaconazole was observed in some patients only after approximately 1 year of therapy. Covariates were not significant. Adverse reactions were observed in 12 patients (15%) (nausea in 5, rash in 5, headache in 1, and lethargy in 1), leading to withdrawal of treatment for 9 patients. *Aspergillus* species were recovered from 22 patients. A posaconazole MIC of >8 mg/L was found in 4 isolates; in 1 of these isolates, this emerged during therapy. Treatment failed in all 4 patients from whom these 4 isolates had been recovered.

Conclusion. Posaconazole is a safe and partially effective treatment for CPA. Prospective comparative studies are now required.

Chronic pulmonary aspergillosis (CPA) is a debilitating syndrome characterized by slowly progressive lung cavitation [1]. The survival rate is ~50% at 1 year in untreated patients [2]. With antifungal therapy, the survival rate at 5 years is ~50%, which comparable to that for many neoplastic diseases [3–4]. CPA typically occurs in patients with preexisting structural lung disease, and it causes significant respiratory and constitutional symptoms [5]. Serial imaging usually reveals progressive pulmonary cavitation, pleural thickening, and/or pulmonary fibrosis. One or more fungal balls may be present within these pulmonary cavities. IgG and/or IgE antibodies against *Aspergillus* species are almost always present, and their detection is a cornerstone for the diagnosis [6–8].

The therapeutic goals for CPA are the prevention of inexorable destruction of the lungs and the minimization of respiratory and constitutional symptoms. Long-term therapy with triazole antifungal agents is the standard of care for CPA [9]. Itraconazole has been extensively used for this purpose, but its use is complicated by toxicity and the emergence of resistance [5, 10, 11]. Voriconazole is an alternative agent, but longer

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Table 1. Clinical and Radiological Criteria Associated with Any Change in a Patient's Clinical Condition

Class	Improvement	Stability	Deterioration[a]
Clinical	• Weight gain of >3 kg • Increased energy levels • Less breathlessness • Increased exercise tolerance	• Not worse or improved • Weight gain of <3 kg • Moderate sputum production • Stable exercise tolerance	• Continued weight loss • Anorexia • Malaise • Lethargy • Hemoptysis, despite bronchial artery embolisation or long remission period • Continuing poor appetite • Worsening cough severity • High sputum load • Worsening, persistent shortness of breath • Symptoms not improving
Radiological	• Reduction of pericavitary thickening • Reduction of pleural thickening • Reduction in cavity size/number • Loss of fungal ball	• No significant change	• Increased pericavitary thickening • Increased pleural thickening • New cavitation • Increased fibrosis with worsening volume loss • New or increasing size of fungal ball

[a] In the absence of concurrent bacterial infection.

term use is frequently complicated by adverse events, such as phototoxicity [12]. The administration of parenteral agents, such as polyenes and echinocandins, is often impractical and extremely expensive. Alternative therapeutic options are urgently required [13].

Posaconazole is a broad-spectrum triazole agent with potent activity against *Aspergillus* species. Posaconazole is a safe and effective agent for the prevention and treatment of a range of invasive fungal infections [14–16]. Here we describe the use of posaconazole for the management of patients with CPA. To our knowledge, this is the first series of patients with CPA who have received posaconazole, and this study represents an important advance for the treatment of this syndrome.

METHODS

Study design. Retrospective clinical data were obtained for all cases of CPA treated with posaconazole at a single centre (National Aspergillosis Centre, University Hospital of South Manchester, United Kingdom). Patients are referred from all over the United Kingdom (populationn ~61 million), with the highest proportion coming from the northwest of England (population ~11 million). Information from case notes, laboratory results, and radiological investigation were compiled using a structured questionnaire. All patients received posaconazole 400 mg twice per day and were advised to take the drug with food.

Definitions. A patient was considered to have CPA if the following findings were present: (1) progressive pulmonary cavitation with associated cavity wall or pleural thickening on chest radiography or cross-sectional imaging, (2) positive *Aspergillus* antibody titer or isolation or visualization of *Aspergillus* species in a biopsy specimen from the lung or pleura, (3) elevated values for inflammatory markers (C-reactive protein level or plasma viscosity), (4) constitutional or pulmonary symptoms lasting for at least 3 months; also required were (5) exclusion of other causes that can mimic this syndrome (eg, *Mycobacterium tuberculosis* infection or pulmonary malignancy) by use of appropriate cultures, serological tests, and additional radiological imaging if required, and (6) no significant systemic immunosuppression (due to uncontrolled human immunodeficiency virus [HIV] infection, haematological malignancy or chronic granulomatous disease, or corticosteroid treatment [>7.5 mg prednisolone per day]). All conditions were required for the diagnosis of CPA. Both clinical and radiological data were used to assess the response to therapy.

Clinical improvement was defined as being present if the patient had weight gain, increased energy levels, reduced breathlessness, and increased exercise tolerance. Radiological improvement was considered present if there was any improvement in the extent of pericavitary and/or pleural thickening, or cavity size and/or number, and loss of any fungal ball. Clinical deterioration was considered present if intercurrent infection was absent and respiratory and constitutional signs and symptoms were progressive. Radiological deterioration was considered present if there was (1) increased pericavitary and/or pleural thickening, (2) new pulmonary cavitation, (3) increased size of existing cavities, (4) progressive pulmonary fibrosis, and/or (5) new or increased size of an intracavitary fungal ball (Table 1.).

A patient was considered to have response to posaconazole

Table 2. Baseline Demographic Characteristics, Underlying Diagnoses, and Clinical Findings Regarding the Extent of Chronic Pulmonary Aspergillosis in the Study Patients

Variable	Primary therapy group (n = 21)	Salvage therapy group (n = 58)	All patients (n = 79)
Demographic characteristic			
Age, years, median (range)	60 (20–78)	62 (38–87)	63 (20–87)
Male sex	13 (69)	32 (55)	45 (57)
Weight, kg, median (range)[a]	54 (34–95)	61 (33–89)	58 (33–95)
Underlying diagnosis			
COPD	7 (33.3)	18 (31.0)	25 (31.6)
Prior pulmonary tuberculosis	5 (23.8)	9 (15.5)	14 (17.7)
Resected non-small cell lung cancer	1 (4.8)	7 (12.1)	8 (10.1)
Bronchiectasis	1 (4.8)	5 (8.6)	6 (7.6)
Sarcoidosis	0	5 (8.6)	5 (6.3)
ABPA	0	5 (8.6)	5 (6.3)
Chronic mild immunosuppression[b]	0	3 (5.2)	3 (3.8)
Previous IPA	0	3 (5.2)	3 (3.8)
Pleural disease	2 (9.5)	1 (1.7)	3 (3.8)
Previous nontuberculous mycobacterial infection	2 (9.5)	0	2 (2.5)
Thoracic cage radiotherapy	1 (4.8)	1 (1.7)	2 (2.5)
Pneumonia	0	1 (1.7)	1 (1.3)
None discerned	2 (9.5)	0	2 (2.5)
Concurrent infection[c]	0	7 (12.1)	7 (8.8)
Clinical and laboratory findings			
Diagnostic test results			
Detectable antibody titer[d]	18/19 (94.7)	50/55 (90.9)	68/74 (91.9)
Aspergillus recovered from culture	5/21 (23.8)	17/58 (28.8)	22/79 (27.8)
Elevated inflammatory marker value[e]	20/20 (100.0)	46/50 (92.0)	65/70 (94.3)
Previous triazole therapy			
Itraconazole	0	53 (91.4)	53 (67.1)
Voriconazole	0	44 (75.8)	44 (55.7)
Radiological findings			
Unilateral	18 (85.7)	47 (81.0)	65 (82.3)
Bilateral	3 (14.3)	11 (18.9)	14 (17.7)
Single cavity	13 (61.9)	40 (69.0)	53 (67.1)
Multiple cavity	8 (38.1)	18 (31.0)	26 (32.9)
Fungal ball	4 (19.0)	16 (27.6)	20 (25.3)
Pulmonary fibrosis	0 (0)	4 (6.8)	4 (5.0)

NOTE. Data are no. (%) or proportion (%) of patients, unless indicated otherwise. ABPA, allergic bronchopulmonary aspergillosis; COPD, chronic obbsrtuctive pulmonary disease; IPA, invasive pulmonary aspergillosis.

[a] Data for 19 patients in the primary therapy group and 42 patients in the salvage therapy group.

[b] Two patients receiving low dosages of prednisolone for rheumatoid arthritis and autoimmune hepatitis and 1 patient with nonmalignant chronic mild neutropenia.

[c] *Pseudomonas* infection or active nontuberculous mycobacterial infection.

[d] Precipitating *Aspergillus* IgG antibody titer.

[e] Elevated C-reactive protein level or plasma viscosity value.

therapy if clinical and/or radiological deterioration were absent. Overall improvement was defined as clinical improvement in the presence of radiographic stability, radiographic improvement in the presence of clinical stability, or combined clinical and radiographic improvement. Treatment-related adverse reactions were defined as any clinical changes attributed to posaconazole by the investigators.

Assessment of response to posaconazole. The time to initial response and time to drug withdrawal due to disease progression or death were estimated using the Kaplan-Meier survival

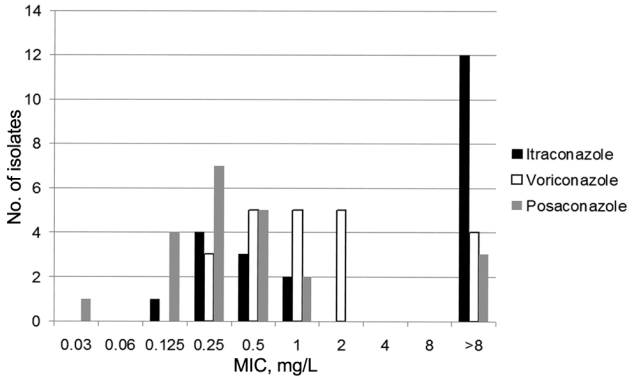

Figure 1. Stacked column chart showing the distribution of minimum inhibitory concentrations (MICs) to itraconazole, voriconazole, and posaconazole at beginning of posaconazole therapy for the 22 *Aspergillus* isolates recovered from patients with positive fungal sputum culture results.

method [17]. Four potential risk factors for lack of response were analyzed: receipt of salvage rather than primary antifungal therapy; presence of an underlying diagnosis; elevated *Aspergillus* precipitin titer prior to therapy; and low first posaconazole serum concentration following initiation of therapy. The impact of these covariates on outcome was assessed using log-rank tests within the R statistical environment [18].

Outcome was assessed following 6 months of posaconazole therapy. Patients were considered to be evaluable if they had received posaconazole for at least 6 months or if they prematurely stopped drug treatment because of an adverse event or death. Therapy was considered successful if the patient had response to posaconazole therapy and had received posaconazole for 6 months. Therapy was considered to have failed if the patient ceased posaconazole therapy because of an adverse event, if the patient died, or if the patient showed no response after at least 6 months of therapy. The Kaplan-Meier analysis suggested that maximal response was obtained after 12 months of therapy; this finding led to a second assessment of patients after 12 months of therapy using identical definitions to those used for the 6-month analysis.

Laboratory methods. Isolates were identified to species level using standard microbiological techniques. Minimum inhibitory concentrations (MICs) to triazoles were determined with EUCAST methodology, with a single modification, which was using a lower final inoculum concentration (0.5×10^5 CFU/mL, rather than $1–2.5 \times 10^5$ CFU/mL) [11, 19]. Posaconazole plasma concentrations were determined using a bioassay, as described elsewhere [20]. *Aspergillus* precipitin titers were measured using a long-established in-house precipitins IgG assay, as described elsewhere [5, 12].

RESULTS

Patient demographic and clinical characteristics. The demographic characteristics and underlying clinical conditions of the 79 patients are summarized in Table 2. Twenty-one patients received primary therapy; 58 patients had stopped prior antifungal therapy because of intolerance (36 patients) or progression of CPA (22 patients). The median age of the patients was 63 years (range, 20–87 years). With the exception of 1 patient from India, all patients were white and were from Britain or Ireland. There were more males than females (45 vs 34).

Chronic obstructive pulmonary disease (COPD), previous pulmonary tuberculosis, and resected non-small cell lung cancer were the commonest underlying conditions. Of the patients with preexisting pleural disease, 2 had asbestos-related pleural disease and 1 had partially resolved spontaneous pneumothorax. Two patients had had thoracic cage radiation therapy (1

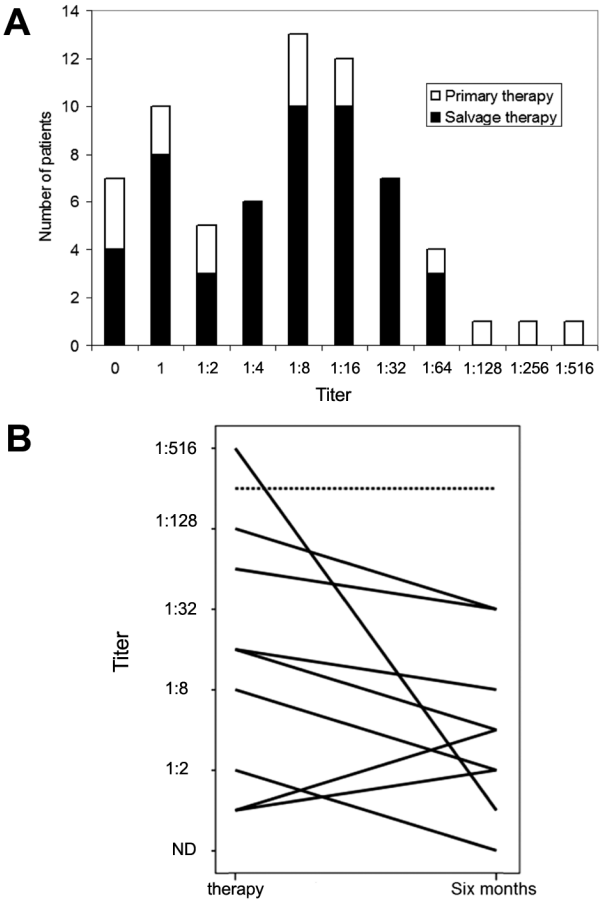

Figure 2. *A, Aspergillus fumigatus* precipitating antibody titers in study patients prior to commencement of posaconazole therapy. *B,* Summary timeline showing changes in the *Aspergillus* precipitating antibody titers in 10 patients treated with primary posaconazole therapy. *Solid line,* responded to posaconazole therapy; *dotted line,* failed to respond to posaconazole therapy. ND, not detected.

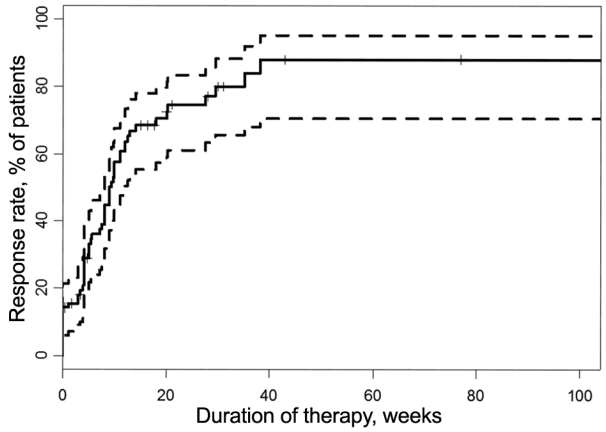

Figure 3. Kaplan-Meier plot showing time to improvement for patients commencing posaconazole therapy. Dotted lines, 95% confidence intervals.

for carcinoma of the breast and 1 for lung cancer). The majority of patients (65 [82%] of 79) had unilateral fungal disease, with two-thirds having a single cavity and a quarter having evidence of a fungal ball. Only 4 patients had evidence of extensive pulmonary fibrosis sufficient to classify them as having chronic fibrosing pulmonary aspergillosis [5]. Four patients were colonized with *Pseudomonas aeruginosa*, and 3 patients were treated for nontuberculous mycobacterial infection (for these 7 patients, posaconazole was second-line therapy). Of the 58 patients given posaconazole as salvage therapy, 53 (91%) had been treated with itraconazole and 44 (76%) had been treated with voriconazole.

Mycological data. Sputum fungal culture yielded a positive result for 22 (28%) of 79 patients and a negative result for 51 (65%) of 79 patients; 6 (8%) of 79 did not produce sputum. Of the 22 patients from whom at least 1 fungal isolate was recovered, 20 had *Aspergillus fumigatus* complex, and 1 each had *Aspergillus flavus* and *Aspergillus nidulans* complex. Of these 22 isolates, 12 had an itraconazole MIC of >8 mg/L and 4 had a voriconazole MIC of >8 mg/L (Figure 1). Eight of the 12 patients yielded an isolate that had an itraconazole MIC of >8 mg/L while being treated with itraconazole; all 8 of these patients subsequently failed to respond to itraconazole therapy. Four of the 12 patients infected with an isolate with an elevated itraconazole MIC had not previously received itraconazole. Three of the 4 patients who had an isolate with an elevated voriconazole MIC had previously been exposed to voriconazole, and all 3 of these patients subsequently failed to respond to voriconazole therapy. Three of 22 patients (ie, all of those in the salvage group) yielded isolates with an initial posaconazole MIC of >8 mg/L. The isolates from these 3 patients had an itraconazole MIC of >8 mg/L and had MICs to voriconazole of 0.25 mg/L, 0.5 mg/L and >8 mg/L.

Precipitating *Aspergillus* IgG titers ranged from undetectable (in patients who were previously treated or who were proven by biopsy to be negative for *Aspergillus* IgG antibody) to 1:516 (Figure 2); 92% of patients had a detectable precipitating *Aspergillus* IgG titer. Initial precipitating *Aspergillus* IgG titers were similar in both groups ($P = .93$; Mann-Whitney U test).

Duration of therapy. The median duration of therapy in the primary therapy group was 28 weeks (range, 4–44 weeks), and in the salvage group it was 31 weeks (range, 1–212 weeks). In the absence of adverse drug reactions or death, the median duration of therapy in the primary grooup was was 29 weeks, and in the and salvage group it was 46 weeks.

Response to therapy. Sixty-seven patients received posaconazole therapy for at least 6 months. A response was seen in 41 patients; 6 patients died, 9 had an adverse event, and 11 showed clinical and/or radiological deterioration. Therefore, at 6 months, posaconazole treatment was successful for 41 (61%) of 67 patients and failed for 26 (39%) of 67. Overall improvement at 6 months was observed in 9 patients (13%). There were 41 evaluable patients at 12 months, of whom 2 had had primary posaconazole therapy. Nineteen of these patients responded to therapy, 7 died, 9 had an adverse event, and 6 showed clinical and/or radiological deterioration. Therefore, at 12 months, posaconazole therapy treatment was successful for 19 (46%) of 41 and failed for 22 (54%) of 41. Overall improvement at 12 months was observed in 6 patients (15%). The 7 patients who died in the first 12 months of posaconazole therapy ultimately succumbed to respiratory failure secondary to pneumonia. There were no instances of massive hemoptysis or nonrespiratory causes of death.

As shown in Figure 3, the Kaplan-Meier plots showed that

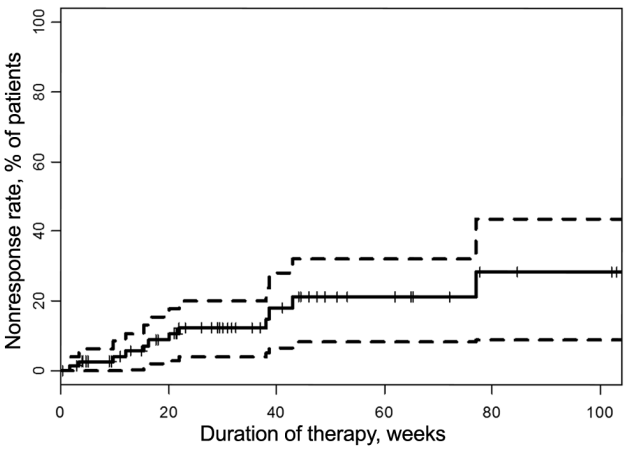

Figure 4. Kaplan-Meier plot showing time to cessation of posaconazole treatment either because of disease progression despite treatment or because of death (not including adverse reactions). Dotted lines, 95% confidence intervals).

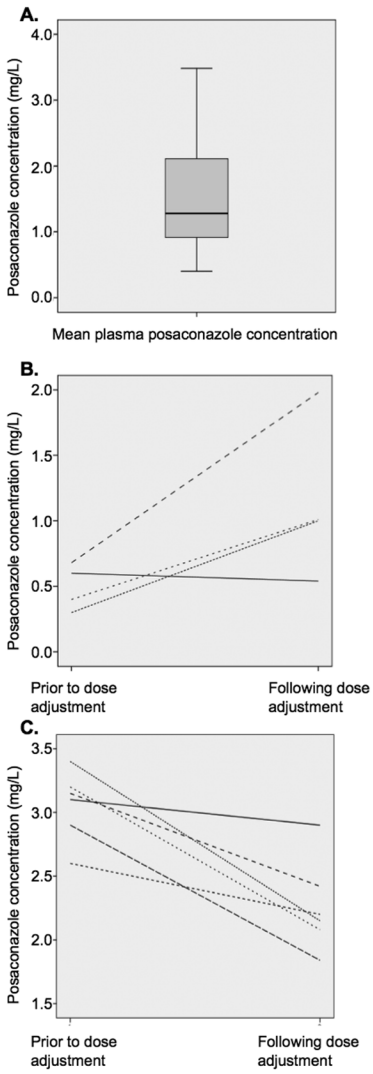

Figure 5. Mean randomly measured plasma concentrations of posaconazole in study patients. *A,* Box plot of mean concentration for 56 patients who received posaconazole 400 mg twice daily without dosage adjustment. *B,* Graph of mean concentration for 4 patients after the posaconazole dosage was increased from 400 mg twice daily to 600 mg twice daily. *C,* Graph of mean concentration for 6 patients after the posaconazole dosage was reduced from 400 mg twice daily to 300 mg twice daily.

~70% of all patients responded (at least temporarily) after 6 months of therapy. This increased to ~85% of patients after 12 months of treatment. Figure 4 shows that after 1 year of therapy, approximately 20% of patients had either stopped treatment or died (from any cause); this estimate increased to approximately 35% at 2 years. None of the potential risk factors examined (receipt of salvage rather than primary antifungal therapy; presence of an underlying diagnosis; elevated *Aspergillus* precipitin titer prior to therapy; and low first posaconazole serum concentration following initiation of therapy) had any statistically significant impact (by log rank test) upon the response to posaconazole by either of these 2 measures.

Of the 3 patients infected initially with isolates that had posaconazole MICs of >8 mg/L, all ultimately failed to respond to therapy. For 1 patient who received posaconazole (as salvage therapy) for 45 weeks, the posaconazole MIC increased from 0.125 mg/L to >8 mg/L, which was associated with clinical and radiological deterioration. Nine patients had an isolate with an itraconazole MIC of >8 mg/L but a posaconazole MIC of ≤1 mg/L. At 6 months, 5 patients had responded to posaconazole treatment, 2 had died, and 2 failed to respond to posaconazole treatment.

Assessment of safety. A total of 13 adverse reactions were observed in 12 (15%) of 79 patients. Nine patients had posaconazole therapy withdrawn because of these adverse reactions. Eight of the 9 patients had stopped posaconazole treatment in the first 3 months and all had ceased posaconazole treatment by 6 months. The most common reaction was nausea (in 5 patients), which led to discontinuation of the therapy in all affected patients. Five patients had cutaneous reactions: 3 developed an acneiform rash, which was severe in 1 patient and required cessation of posaconazole treatment. One patient stopped treatment following a significant worsening of psoriasis. One patient developed minor erythema on the limbs and torso; treatment was continued, and the rash resolved. One patient developed cholangiocarcinoma that required a biliary stent; this was thought unlikely to be related to posaconazole therapy.

Thirty-six patients received posaconazole because of an adverse reaction to either itraconazole or voriconazole. There were 7 patients who had triazole-associated peripheral neuropathy. Deterioration of neuropathic symptoms was not observed with posaconazole therapy. There were 13 patients who had rash (12 from voriconazole and 1 from itraconazole therapy); of these patients, only 1 patient with a rash secondary to treatment with voriconazole also developed a rash while receiving posaconazole. There were 4 patients with deranged liver function tests (3 receiving voriconazole and 1 receiving itraconazole), but none of these patients had a recurrence of hepatitis with posaconazole treatment.

Therapeutic drug monitoring. At least 1 measurement of the plasma posaconazole concentration was obtained for 66 of the 79 patients. Posaconazole concentrations were randomly measured after 1 month of therapy, and the measurement was repeated every 3–6 months. Fifty-six patients continued to receive posaconazole at a dosage of 400 mg twice daily throughout their treatment. The median value for the random plasma posaconazole concentrations was 1.28 mg/L (range, 0.42–3.48 mg/L) (Figure 5). Ten patients had their dosage of posaconazole modified (by increasing to 1200 mg daily or reducing it to 600

Table 3. Summary of the Methods and Outcomes of Treatment Studies Involving Patients with Chronic Pulmonary Aspergillosis

Agent, study	Year	Drug dose	Route of administration	Study design	Duration of follow up	No. of patients treated	Overall response rate, % of patients	Adverse reaction rate, of patients
Itraconazole								
De Buele et al [23]	1988	100–400 mg	Oral	CS	Unknown	86	60	NA
Dupont [24]	1990	200 mg–400 mg	Oral	CS	Mean, 10.9 months	28	93	NA
Campbell et al [21]	1991	200 mg	Oral	CS	6 months	9	29	NA
Caras et al [22]	1996	400 mg	Oral	CS	5–12 months	3	67	NA
Saraceno et al [25]	1997	200–400 mg	Oral	CS	4–14 months	6	67	33
Tsubura [26]	1997	100–200 mg	Oral	CS	Not known	49	63	18
Denning et al [5]	2003	400 mg	Oral	CS	12 days to more than 10 years	17	71	18
Nam et al [3]	2009	unclear	Oral	CS	Median, 6 months	26	38	NA
Overall						224	63	19
Amphotericin B								
Denning et al [5]	2003	0.5–1 mg/kg	IV	CS	12 days to more than 10 years	11	82	64
Nam et al [3]	2009	NA	IV	CS	Median 6 months	4	0	NA
Overall						15	60	64
Micafungin								
Kohno et al [31]	2004	25–150 mg	IV	CS	11–57 days	22	55	NA
Izumikawa et al [30]	2007	150–300 mg	IV	CS	More than 4 weeks	9	78	11
Saito et al [28]	2009	150–300 mg	IV	RCT	4 weeks	50	60	26
Yasuda et al [32]	2009	NA	IV	CS	Long term	26	58	NA
Overall						107	63	24
Voriconazole								
Denning et al [5]	2003	400 mg	Oral	CS	12 days to more than 10 years	2	50	50
Jain et al [12]	2006	400 mg	Oral	CS	3 months	16	56	31
Sambatakou et al [29]	2006	400 mg	Oral	CS	4–24 weeks	15	80	19
Camuset et al [27]	2007	400 mg	Oral	CS	6 months	24	58	13
Saito et al [28]	2009	4 mg/kg	IV	RCT	4 weeks	46	59	61
Philippe et al [33]	2009	200 mg	Oral	CS	6 months	41	44	17
Overall						101	61	35

NOTE. CS, case series; IV, intravenous; NA, not available; RCT, randomized controlled trial.

mg daily) that led to a corresponding change in serum posaconazole concentration (Figure 5).

DISCUSSION

Chronic pulmonary aspergillosis is an insidious and relentlessly progressive syndrome. There is substantial disease-related morbidity, and the 5-year mortality rate is comparable to that for many malignancies. There are few therapeutic options, and current regimens are complicated by drug-associated toxicity and antifungal resistance. Because this infection is relatively uncommon, large randomized clinical trials have not been performed, and there is considerable uncertainty about optimal regimens. This study presents one of the largest series of patients with CPA receiving an antifungal agent and provides a basis for the future systematic study of this neglected syndrome.

As is the case for acute invasive fungal infections, an objective assessment of the therapeutic response in patients with CPA is difficult. An improvement in signs and symptoms may take many months. Radiological appearances typically change slowly and the extent of improvement is frequently subtle. The importance of improvement in serologic test results is unknown. Sometimes subtle antifungal drug side effects can mask or confound an assessment of response (eg, gastrointestinal intolerance leading to weight loss or fatigue associated with itraconazole therapy). Currently, there are no standardized definitions to measure either the severity of CPA or response to therapy. Clearly, these definitions would facilitate future studies. Our results suggest that the duration of therapy has an important bearing on the response rate, and 6 months is probably a reasonable period of time to assess the response to antifungal therapy in future clinical trials. The underlying respiratory disease may also be an important determinant of the overall re-

sponse because this may be inactive (eg, previous pulmonary tuberculosis) or active (eg, emphysema).

Posaconazole is a triazole with potent broad-spectrum antifungal activity. Its efficacy has been demonstrated for the prevention of invasive fungal infections in profoundly immunocompromised hosts and for treatment of patients failing treatment with or intolerant of other antifungal agents [14–16]. In this study, the response rates for patients with CPA to posaconazole after 6 and 12 months of therapy were 61% and 46%, respectively. These estimates are comparable to those obtained with itraconazole (which range from 29% to 93% [3, 5, 21–26]) and voriconazole (which range from 44% to 86% [5, 12, 27–29]) (Table 3). Treatment was least successful using itraconazole at a dosage of 200 mg daily [21] and more successful using a dosage of 400 mg daily [5, 22, 25]. Of the echinocandins, only micafungin has been studied; the success rate in 4 studies ranges from 55% to 73% [28, 30–32]. The relatively wide range of estimates for response likely reflects differences in the duration of therapy, sample size, drug exposure and definitions of response. This variability provides a further impetus to standardize definitions of therapeutic outcome.

Posaconazole therapy appears to be well tolerated. While itraconazole and voriconazole are both effective agents, their broad clinical utility is limited by a relatively high incidence of adverse events [10, 12]. While many of these are fully reversible, they usually preclude the future use of that agent. However, an adverse event to one triazole does not necessarily preclude the use of another. The lack of recurrence or progression of peripheral neuropathy, rash, and hepatitis caused by other triazoles is noteworthy.

Long-term triazole therapy is also compounded by increasing reports of triazole resistance [11]. One issue this study addresses is whether the development of itraconazole or voriconazole resistance precludes the use of posaconazole. Most target site mutations result in an elevated posaconazole MIC, in some instances as high as >8 mg/L [11]. In our study, a response to posaconazole therapy was seen in ~50% of patients with an isolate that had an itraconazole MIC of >8 mg/L but a posaconazole MIC of ≤1 mg/L. All patients infected with an isolate that had a posaconazole MIC of >8 mg/L failed to respond to therapy. We are unable to derive clinical breakpoints for CPA because MIC data was only available isolates from 20 patients who were culture positive and had received at least 6 months of treatment.

The magnitude of drug exposure in the serum and various intrapulmonary subcompartments (eg, the pulmonary cavity) that is associated with near-maximal antifungal effect is unknown. Furthermore, there is no information on the relationship between drug concentration and the emergence of antifungal resistance. We routinely perform therapeutic drug monitoring and aim to keep random serum posaconazole concentrations at >0.5 mg/L, although we may modify these targets with the advent of further clinical information [16]. An intravenous formulation of posaconazole may facilitate induction therapy for patients with extensive active disease. Newer oral formulations with improved oral bioavailability may further improve the therapeutic response and minimize the emergence of antifungal resistance.

In conclusion, posaconazole is at least as effective as other agents for CPA. Furthermore, this compound is well tolerated and can be used for patients with adverse events to other triazoles. A successful clinical response may be observed for some patients infected with isolates that have elevated MICs for other triazoles. Randomized clinical trials are now required to further optimize the clinical outcome of this debilitating and neglected syndrome.

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