The contribution to carbon dioxide removal by the $AVCO_2R$ system was demonstrated when the device was clamped for the apnea challenge. The $PaCO_2$ rose to 68 mm Hg after the circuit was clamped, and the patient was maintained on just the oscillator. After the AVO_2R was restarted, the $PaCO_2$ dropped to 44 mm Hg, with normalization of the arterial pH. At no time did this system alter mean arterial pressure.

The device was easily set up at the bedside and maintained without additional nursing or respiratory therapy resources. Because $AVCO_2R$ does not require a pump and uses a less-complicated circuit, the full ECMO team was not required, and the system was primed and inserted by one physician.

CONCLUSION

$AVCO_2R$ was an effective method of controlling pH and $PaCO_2$ in a heart-beating organ donor that suffered severe respiratory failure that could not be maintained with standard or unconventional ventilator techniques.

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SALVAGE THERAPY WITH VORICONAZOLE FOR INVASIVE FUNGAL INFECTIONS IN PATIENTS FAILING OR INTOLERANT TO STANDARD ANTIFUNGAL THERAPY

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Background. **Invasive fungal infections (IFI), particularly those caused by *Aspergillus* and other angioinvasive molds, are associated with an excessive mortality despite therapy.**

Methods. **Voriconazole was prescribed on a compassionate basis to patients with IFI who were intolerant to or who had progressed despite standard therapy. Outcome was determined by protocol-based criteria as established by the consensus definitions (complete response [CR], partial response [PR], stable disease, failure, and intolerance).**

Results. **Forty-five patients were enrolled in a compassionate release program (29 [64%] because of failure of response to standard therapy), between 1998 and 2002. Of the 45 patients enrolled, 35 (78%) had invasive *Aspergillus*, 3 (7%) had *Fusarium*, and 2 (4%) had *Scedosporium* infections. Underlying illnesses were as follows: 13 (29%) solid-organ transplant (SOT), 11 (24%) BMT, and 7 (13%) hematologic malignancy. Site of infection was as follows: 26 (58%) pulmonary, 9 (20%) disseminated, 5 (11%) central nervous system (CNS), and 3 (7%) sinus. Overall response rates were as follows: 9 (20%) CR, 17 (38%) PR, 15 (33%) failure, and 4 (9%) intolerant. Seven of the eight (88%) patients with sinus or CNS disease demonstrated stabilization of the IFI. The median duration of voriconazole therapy was 79 days with 9 (20%) patients receiving over 1 year of therapy. Nine thousand one hundred twenty-eight days of therapy were given with only four serious adverse events in two cases considered possibly or probably drug related.**

Conclusions. **In this population of severely immunocompromised patients with life-threatening IFI who have failed or were intolerant to standard antifungal therapy, voriconazole demonstrated substantial efficacy and an acceptable level of toxicity.**

Invasive mold infection in compromised hosts constitutes a therapeutic emergency. In particular, angioinvasive mold infections are associated with extremely poor outcomes, with an overall response rate to therapy of invasive *Aspergillus* infection of 37% (*1–3*). These infections typically threaten the most vulnerable patients: those undergoing cancer chemotherapy, bone marrow transplantation (BMT), or solid-organ transplantation (SOT). Because immunosuppressive therapy is being used more aggressively and more successfully for an increasing number of conditions, the incidence of invasive fungal infections (IFI) is increasing. *Aspergillus* is the prototype angioinvasive pathogen, with its invasion of blood vessels having three major effects: hemorrhage, infarction, and metastases. An important factor in the poor results observed in the therapy of these infections is that 50% of patients have

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metastatic disease at the time of first diagnosis. Thus, it is not surprising that immunocompromised patients with invasive aspergillosis (IA) have a very high mortality (*2*, *4–7*). For example, in neutropenic cancer patients and allogeneic BMT patients, the mortality from IA approaches 90% and is even higher if central nervous system (CNS) involvement has occurred (*1*, *2*, *8*, *9*). Amphotericin preparations have been the standard therapy for IFI for several decades. With the advent of newer therapies, it is appropriate to assess the utility of these newer agents in patients for whom therapy has been ineffective or toxic.

Voriconazole has demonstrated fungicidal activity against many of the clinically relevant molds (*10–12*) and has demonstrated substantial clinical activity in the treatment of IA (*13*, *14*) and as salvage therapy for IFI in children (*15*). Little is known about voriconazole as salvage therapy for IFI in adults. Voriconazole has several important attributes, including availability as both an intravenous and oral preparations as well as a limited toxicity profile that has allowed prolonged outpatient therapy. We report a multi-institutional experience of 45 patients treated with voriconazole as therapy for IFI in the setting of intolerance to standard therapy or as salvage therapy.

METHODS

All patients treated at our institutions (Brigham and Women's Hospital, Dana-Farber Cancer Institute, and Massachusetts General Hospital) with open-label compassionate release voriconazole are presented. Eligibility for enrollment required all patients to (1) have a probable or proven IFI, and (2) the patient had to have failed standard antifungal therapy, was intolerant to standard antifungal therapy or, had an infection with an organism for which there is no licensed therapy. A confirmed IFI was defined as per the consensus definition (*16*). If infection was discovered at more than one site, the site of infection carrying the worst prognosis was considered in the analysis (e.g., disease in the lung and brain is considered a CNS infection). Disseminated disease was defined as infection at more than one site without CNS or sinus involvement. Failure of standard antifungal therapy was defined as progression of the infection either clinically or radiographically despite 7 days or more of standard antifungal therapy. Intolerance to treatment with standard antifungal therapy was defined as either persistent, debilitating drug-related symptoms or clinically significant deterioration of renal function. Institutional review board approval for this study was obtained.

Voriconazole was given as a loading dose of either 6 mg/kg intravenous q12 hr x 1 day or 400 mg orally q12 hr x 1 day, followed by maintenance therapy of either 4 mg/kg intravenous q12 or 200 mg po bid orally. The dosage was adjusted to a loading dose of 200 mg po q12× 2 followed by 100 mg po q12 hr if the patient weighed less than 40 kg. At the discretion of the responsible physician, the maintenance dose was increased to 300 mg po bid (or 200 mg po bid if weight less than 40 kg) for refractory infections. Duration of therapy was at the discretion of the treating physician and data was censored as of December 1, 2002. Clinical data were available on all patients for at least 90 days after the initiation of therapy. All patients were seen daily while inpatients and at least monthly in the outpatient setting by study staff. Each patient received an individualized treatment plan including meticulous immunosuppressive management, surgical debridement, control of permissive viral infections, and combination antifungal therapy at the discretion of the treating infectious disease specialist. Patients on rapamycin were excluded because of the potential of clinically important drug interaction, and intravenous therapy was avoided in patients with significant renal dysfunction (because of the risk of accumulation of the excipient cyclodextran).

Efficacy was evaluated by a global assessment of clinical, radiographic, and microbiologic response. Responses were defined according to the following criteria: complete response (CR), resolution of all attributable signs, symptoms, and radiographic abnormalities present at baseline with mycologic eradication; partial response (PR), greater than 50% improvement in attributable signs, symptoms, and radiologic abnormalities present at baseline; failure because of death but stable disease, persistence of disease without evidence of significant progression or regression for at least 14 days and eventual death related to complications of the underlying illness (e.g., graft-versus-host disease [GvHD]); failure disease progression, deterioration in attributable signs, symptoms, or radiologic abnormalities or death; and discontinuation, intolerance of study medication.

RESULTS

Forty-five patients were initiated on compassionate release voriconazole between May 1998 and July 2002. The mean age of these patients is 65 years, and 62% (28) were male. As seen in Tables 1 and 2, the underlying illnesses in this group were predominantly status-postBMT (24%), leukemia (13%), and status-postSOT (29%). Most of the patients in the "other" category received corticosteroids, and all had significant underlying comorbid illnesses such as sarcoidosis, lupus, cystic fibrosis, bronchiectasis, diabetes, Crohn's disease, or chronic granulomatous disease. The indication for voriconazole was progression of the underlying fungal infection in 28 (62%), intolerance to standard antifungal therapy in 16 (36%), and primary therapy in 1 (2%). The nature of the intolerance was increased creatinine in 13 (81%) and nausea, stereotypic lower back pain, and decreased platelet count, each occurring in a single patient. The median duration of treatment was 79 (range 1–1,041; IQR 30–298 days) days, with 9,128 days of therapy given.

The site of infection was the lung in 28 (62%), sinuses in 3 (7%), CNS in 5 (11%), blood stream in 2 (4%), peritoneum in 1 (2%), skin–soft tissue in 2 (4%), and multiple sites in 4 (9%). As seen in Table 2, the organisms identified can be divided into 3 categories: *Aspergillus* (*A fumigatus* in 18 [40%], *A niger* in 2 [4%], *A flavus* in 1 [2%], and *Aspergillus species* in 13 [29%]), new and emerging mycoses (*Fusarium species* in 3 [7%], *Ochroconis gallapopavum* in 1 [2%], and *Scedosporium prolificans* in 1 [2%]), and relatively resistant yeast species (1

TABLE 1. Patient characteristics

Age (years)	
Mean	65.1
Median	53
Range	20–81
Sex	
Male (%)	28 (62)
Female (%)	17 (38)
Reasons for enrollment	
Primary antifungal therapy (%)	1 (2)
Refractory to conventional antifungal therapy (%)	28 (62)
Intolerance to conventional antifungal therapy (%)	16 (36)
Duration of previous antifungal therapy	
>7 days (%)	42 (93)
>30 days (%)	32 (71)
Duration of voriconazole therapy	
Median (days)	79
IQR (days)	30, 298
>1 year (%)	9 (20)

IQR, ●●●.

TABLE 2. Type of invasive fungal infection by underlying host risk factor

Pathogen	No. of infections	Heme Malig	BMT	Other Malig	SOT	Other
Aspergillus sp.	35	4	10	4	9	8
Other mold	6	2	1		2	1
Resistant yeast	4	1			2	1
Total (%)	45	7 (16)	11 (24)	4 (9)	13 (29)	10 (22)

One patient each had two pathogens identified: *A fumigatus*/*S apiospermum* and *Fusarium*/*T beiglii*. These two cases were considered in the *Aspergillus* and *Fusarium* categories, respectively.

Heme Malig, hematologic malignancy; BMT, bone-marrow transplantation; Other Malig, other malignancy; SOT, solid-organ transplantation; Other, other predisposing illnesses.

[2%] each of *Candida krusei*, *Candida parapsilosis*, *Torulopsis glabrata*, *Malassezia furfur*). One patient each had two organisms identified: *Fusarium–T beiglii* and *A fumigatus–S apiospermum* and were considered in the "other mold" and *Aspergillus* categories, respectively, in the analyses. Outcomes in these two cases were intolerance to voriconazole on day 23 and PR, respectively. Voriconazole was given as primary therapy in one case (*Fusarium–T beiglii* combination infection), after fluconazole in two cases (*C parapsilosis* and *T glabrata* infections), after itraconazole in one case (*A niger*), and the remainder after an amphotericin-based regimen. Preceding systemic antifungal therapy was given for at least 7 days in 42 (93%) patients and over 30 days in 32 (71%) patients. Adjuvant surgery was performed in seven patients, and two patients underwent a diagnostic–partially therapeutic video assisted thoracoscopic surgery.

Combination antifungal therapy with voriconazole was given to 10 patients, 9 of whom had *Aspergillus* infection. Voriconazole was given with caspofungin in five, with AmBisome in two, and with both caspofungin and AmBisome in three (an example of the complexity of this patient population is reported in detail elsewhere) (*17*). Three patients with advanced disease expired within 11 days of instituting voriconazole, likely from progressive infection (2 on three-drug therapy and 1 on caspofungin–voriconazole). Three patients had stabilization of their IFI but succumbed to their underlying illness 30, 33, and 76 days later. The remaining four patients all had a PR to combination therapy and have remained on voriconazole long-term therapy.

A favorable response (CR or PR) was seen in 26 (58%). Failure of therapy occurred in 15 (33%) patients: 3 with progressive fungal infection, 3 with GvHD, 2 with progressive leukemia, 2 with bacterial sepsis, 1 caused by complications during neutropenic period of BMT, 1 with renal failure, 1 with pneumonia, 1 with multi-organ system failure, and 1 with pulmonary embolism. Table 3, top and middle, demonstrate the reason for compassionate release and success of therapy by underlying medical condition. Fifteen of 28 (54%) patients who received voriconazole because of efficacy failure of previous antifungal therapy and 11 of 16 (69%) patients treated because of intolerance to the initial antifungal therapy had a favorable response. There was no significant difference in clinical response on the basis of the patient's underlying medical condition.

A favorable clinical response was seen in patients with *Aspergillus* pulmonary and sinus infection and "other mold" infection, 62%, 50%, and 83% of the time, respectively, Table 3, bottom. Patients who failed therapy fell into two2 patterns: (1) rapidly progressive disease that typically lead to death within days of starting therapy (8/15 [53%] of failures) and (2) those who had stabilization of their fungal infection but succumbed to complications of their underlying medical illness (7/15 [47%] of failures). Patients who failed but had stabilization of the IFI lived 30 to 790 days after initiating voriconazole (Fig. 1).

There were eight patients with *Aspergillus* sinus or CNS disease: three responded clinically, three were considered treatment failures, and two were treatment intolerant. The three treatment failures all had stabilization of their IA despite aggressive immunosuppression for GvHD and survived between 30 and 399 days, when all succumbed to complications of GvHD. One patient, with sinus infection, died on day 30 of voriconazole therapy with no clinical disease progression during this time period; at autopsy, fungal forms were noted to be present in the sinus. In the two voriconazole-intolerant patients, therapy was discontinued on days 7 and 363 of treatment. Thus, benefit of voriconazole therapy was seen in 7 of 8 (88%) patients.

Six patients subsequently required further cancer chemotherapy, including five allogeneic BMT patients and one patient who required treatment of posttransplant lymphoproliferative disorder. These patients had confirmed aspergillosis (3), *Fusarium* (1), *C krusei* (1), and mold (1). None of these patients developed any evidence of recrudescent fungal infection during the subsequent chemotherapy treatment while being maintained on a prolonged course of voriconazole.

Safety

Among 45 patients treated for 9,128 days, 82 serious adverse events (SAEs) occurred in 27 of these patients. Only four of these SAEs, occurring in two patients, were considered possibly (*3*) or probably (*1*) related to study medication (nausea and vomiting and pericarditis in 1 patient and change in mental status and increased liver-function tests in the other). Only the SAE of increased liver-function tests resulted in the discontinuation of voriconazole. The three possibly related SAEs responded to dose reduction or temporary discontinuation of study medication, with judicious reintroduction.

There were four AEs which required discontinuation of study medication: increased liver-function tests in four, rash and increased liver-function tests in one, and atrial fibrillation in one at 363, 19, 7, and 23 days, respectively. These abnormalities resolved in all four patients with the cessation of voriconazole. Thus, our adverse event rate requiring discontinuation of therapy is 9%. Given the complexity of care these patients require, it is often difficult to ascribe side effects precisely. The patient who was discontinued on therapy because of rash and increased liver-function tests was

TABLE 3. Reason for compassionate release and success of therapy by underlying medical condition

	No.	CR	PR	Failed SD	Failed DP	Intolerance
Reason for enrollment[a]						
Primary Therapy	1					1
Efficacy Failure	28	5	10	11		2
Intolerance	16	4	7	4		1
Total	45	9	17	15		4
Primary underlying condition[b]						
Heme Malig	7	1	2	1	2	1
BMT	11	1	6	3		1
Other Malig	4	1	2		1	
Other	10	2	4	1	2	1
SOT	13					
Lung		2	3	1	1	
Liver					2	
Cardiac		1				
Renal		1		1		1
Total (%)	45	9 (20)	17 (38)	7 (16)	8 (18)	4 (9)
Type of fungal infection[c]						
Aspergillus						
Pulmonary	25	4	12	4	5	
CNS	5	1		2		2
Disseminated	2				1	1
Sinus	3	1	1	1		
Other mold	6	1	4			1
Resistant yeast	4	2			2	
Total	45	9 (20)	17 (38)	7 (16)	8 (18)	4 (9)

[a] Clinical response by reason for enrollment. CR, PR, or failed SD, patient survived for greater than 30 days but succumbed to the underlying disease with clinical and radiographic stabilization of the fungal infection; failed DP, patient died within 30 days of beginning voriconazole therapy or had evidence of progression of the fungal infection.

[b] Clinical response by underlying condition.

[c] Response by type and site of invasive fungal infection.

SOT, solid-organ transplantation; CR, complete response; PR, partial response; failed SD, stable disease: patient survived for greater than 30 days but succumbed to the underlying disease with clinical and radiographic stabilization of the fungal infection; failed DP, disease progression: patient died within 30 days of beginning voriconazole therapy or had evidence of progression of the fungal infection; Heme Malig, hematologic malignancy; BMT, bone-marrow transplant; CNS, central nervous system.

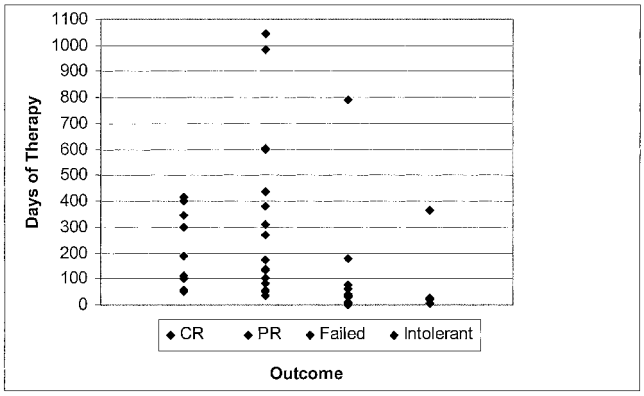

FIGURE 1. Outcome and duration of therapy. Prolonged therapy (often >1 year) in the 26 successfully (complete response [CR]/partial response [PR]) treated patients and time to failure of therapy or cessation of therapy caused by intolerance in the remaining 19 treated patients. Many of the patients who failed or were intolerant of voriconazole survived for more than 30 days and had stabilization of the invasive fungal infections (IFI) (considered failure stable disease in the analyses).

subsequently resumed voriconazole therapy without difficulty. No significant visual abnormalities were noted.

Sixteen patients received voriconazole because of intolerance of standard antifungal therapy, 13 of whom had a significant elevation of creatinine because of amphotericin therapy. In these 13 patients, 2 expired within 1 week, and the creatinine returned to baseline in the remaining 11 patients at a median of 8 (range 3–32, IQR 7–18 days) days. Calcineurin inhibitors were used in 21 (47%) patients concurrently. Daily dosages were reduced by approximately 20% to 70% of patients on tacrolimus (n=11) and 40% to 60% of those on cyclosporine (n=10). Close monitoring of calcineurin levels allowed proper dosage adjustments (with initiation and termination of voriconazole therapy and with changes in renal function) to be performed safely, with no associated adverse events noted (such as renal dysfunction).

DISCUSSION

This experience demonstrates substantial efficacy of voriconazole as salvage therapy for IFI in adult patients, with a minimum response rate of 58%. These data add to the growing database on the treatment of IFI, especially IA, with voriconazole having comparable efficacy in this setting as it does in the primary therapy of IA where 53% and 48% response rates have been reported by Hebrecht et al. (*14*) and Denning et al. (*13*), respectively. In the setting of salvage therapy for IFI, these results compare favorably with the data for caspofungin (*18–20*) (36% response rate: 19 of 53 patients and the basis for FDA approval as a therapy for refractory IA), itraconazole (*21*) (39–63% response rates re-

ported), and voriconazole (*15*) in pediatric patients (45% response rate). Specifically, the data presented in this report on voriconazole compares favorably with the caspofungin salvage data presented to the FDA for product approval, where therapeutic success (CR/PR) of caspofungin was seen in 50% of hematologic malignancy, 17% of BMT, and 38% of SOT patients and in 47% of pulmonary, 23% of disseminated, and 25% of sinus/CNS infections (*20*).

Voriconazole has many drug-drug interactions, which is of especial concern in patients undergoing organ transplantation (*12*, *22*, *23*). Because voriconazole is a potent inhibitor of the P-450 enzyme system, especially CYP2C9, 3A4, and 2C19, the interaction with calcineurin inhibitors are especially important, with dose reductions of 50% for cyclosporine and 67% for tacrolimus in the setting of voriconazole use typically required (*12*); however, substantial patient-to-patient variability requires close monitoring of calcineurin blood levels, especially with the institution and cessation of voriconazole therapy. In BMT patients, there is a bimodal risk for IFIs during the neutropenic period and subsequently in the setting of GvHD (*6*, *24*, *25*). The occurrence of GvHD is analogous to rejection periods in SOT, with the greatest intensity of immune suppression, substantial risk for infection, and significant exposure to multiple medications (*26*). In the transplant patients treated in this report, close monitoring of calcineurin drug levels was performed, and no complications from drug-drug interactions were noted.

A significant challenge in determining therapeutic efficacy in this medically complex patient population is the high mortality related to the underlying illness (e.g., grade III/IV GvHD). This impairs the ability to determine the treatment effect of a new therapy on a single aspect of the patient's illness (e.g., fungal infection). In this report, therapeutic failure was associated with death in 14 of 15 (93%) patients. In 7 of these 15 patients, a clinical benefit of voriconazole in controlling the IFI was noted with fungal disease stabilization despite the patients typically requiring increased immunosuppression and eventually succumbing to their underlying condition over the course of weeks to months. In addition, one of the four patients who discontinued voriconazole therapy because of intolerance (increased liver-function tests) was able to tolerate the study medication for 363 days with improvement of the IFI. Thus, significant clinical benefit was seen in an additional nine patients, with an overall response rate of 78% (35 of 45 patients).

Of the 28 patients treated because of failure of standard antifungal therapy, 15 (54%) had a PR or CR to voriconazole, and 11 (39%) were considered failures. Six of the 11 clinical failures achieved stabilization of the IFI but succumbed to other complications of their underlying illness. Thus, we believe the true response rate in this group is 21 of 28 (75%). In those patients with IA failing standard therapy, the overall response rate of voriconazole was 54%, whereas 74% received some benefit with stabilization of the IFI despite progression of the underlying illness. Although the experience is limited, response of infections caused by emerging mycoses was encouraging, with two of two patients with *Scedosporium* infection responding (PR or CR), and two of three patients with *Fusarium* responding with the third intolerant of voriconazole therapy. These data suggest the utility of voriconazole in the therapy of these pathogens.

Management of CNS or sinus aspergillosis is extremely challenging, with a nearly 100% mortality (*8*, *20*, *27*). The experience presented here suggests a more favorable outcome with 7 of 8 (88%) patients demonstrating a favorable clinical response. Because the CNS is a pharmacologically privileged site, and therapeutic failures are common, these data strongly suggest that voriconazole should be considered when sinus or CNS infection is diagnosed. Another high-risk group of patients with historically poor outcomes are those who require further intensive chemotherapy in the setting of an active IFI. Five patients who were treated for an IFI subsequently required an allogeneic BMT, and none had recrudescent fungal infection. All five patients were maintained on voriconazole throughout the transplant period.

Voriconazole was well tolerated in this complex patient population, with 45 treated patients receiving 9,128 days of therapy. The median duration of therapy was 79 days. Nine patients received over 1 year of therapy, three of whom have received more than 2 years of treatment. Unlike pyogenic infection, the treatment of invasive mold infections requires prolonged therapy, especially when the host immune defect cannot be corrected (e.g., GvHD, SOT). The successful outcome reported here is in part caused by the ability to provide prolonged therapy with limited toxicity. Only four patients required discontinuation of voriconazole because of clinically significant AEs thought to be possibly or probably related to study medication. In addition, those patients requiring voriconazole because of amphotericin-B associated renal dysfunction had a return to baseline creatinine typically within 8 days.

There are several likely contributing factors to the success of voriconazole in this setting including tolerability, oral formulation allowing prolonged therapy, and excellent antifungal activity. These data further confirm the clinical activity of voriconazole in the treatment of IFI and demonstrates the important role of this agent in salvage therapy.

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