

Efficacy and Safety of Amphotericin B Lipid Complex for Zygomycosis

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A multicenter, postmarketing database was used to evaluate the efficacy and safety of amphotericin B lipid complex (ABLC) as treatment of invasive zygomycosis in 64 immunocompromised patients. Overall, 46 patients (72%) responded to ABLC. Response rates were higher in patients who received first-line ABLC (80%) than in patients who received ABLC as second-line therapy (69%) or patients with preexisting renal disease (78%). Renal function stabilized or improved in the majority of patients, including those with preexisting renal disease. These results suggest that ABLC is effective as first- and second-line therapy in patients with zygomycosis and is less nephrotoxic than conventional amphotericin B. [*Infect Med.* 2003;20:201-206]

Key words: Amphotericin B lipid complex ■ Nephrotoxicity ■ Zygomycosis

Z ygomycosis, an opportunistic and potentially fatal infection, is one of the most difficult-to-treat invasive fungal infections. The combination of early diagnosis, surgical debridement, and amphotericin B therapy reduces the high mortality rate associated with zygomycosis, but the renal and systemic effects of conventional amphotericin B (amphotericin B deoxycholate) may limit its use. Amphotericin B lipid complex (ABLC) has been shown to produce similar or better response rates than those produced

by conventional amphotericin B, and with less nephrotoxicity.

Zygomycosis typically involves the rhino-facial-cranial areas, lungs, skin, or GI tract, but the organism may disseminate through the bloodstream.¹ Rhinocerebral disease, the most common form of zygomycosis, is characterized by paranasal sinus infection, which can extend to the orbit, hard palate, and brain.² Pulmonary zygomycosis is less commonly encountered, and it usually presents as a rapidly progressing pneumonia.

Predisposing factors for zygomycosis include diabetes mellitus (especially ketoacidosis), prolonged corticosteroid therapy, iron overload states, hematologic and other malignancies, and other immunosuppressive states.³⁻⁵ Primary cutaneous zygomycosis is caused by *Rhizopus* species and usually develops as a localized necrotic cellulitis.⁶ This type of zygomycosis generally results from the use of contaminated bandages or needles, and most patients do not have any other predisposing conditions.

Zygomycosis is highly aggressive and is associated with significant mortality rates. Rhinocerebral zygomycosis was previously considered uniformly fatal. Early diagnosis combined with aggressive surgical debridement and medical treatment has resulted in survival rates of up to 89% in some patient populations.^{7,8}

The nature of the underlying disease is the most important determinant of survival in these patients. Immunocompetent patients have the highest survival rates (75%), followed by patients with diabetes (60%) and patients with other systemic disorders (20%), such as cancer. The overall survival rate for patients with pulmonary zygomycosis was reported to be 44% in patients with various risk factors.⁹ The mor-

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tality rate associated with GI zygomycosis is very high (98%), primarily because this infection is difficult to diagnose early in the course of the disease.¹⁰

Although conventional amphotericin B has been the traditional choice of first-line treatment for invasive fungal infections, the renal and systemic toxicities associated with it often limit its use. A lipid

formulation of amphotericin B, ABLC, was developed to reduce toxicity and improve the efficacy associated with conventional amphotericin B therapy.

The purpose of the study described in this article was to assess the efficacy and safety of first- and second-line ABLC therapy in patients with zygomycosis, particularly patients with underlying renal

disease, using a multicenter, post-marketing database, the Collaborative Exchange of Antifungal Research (CLEAR) database.

Methods

The CLEAR database was searched to identify patients with zygomycosis who received ABLC after it became commercially available in the United States (January 1996) and Canada (July 1997). Through December 1999, 186 institutions submitted data for 3411 patients. To have been included in the CLEAR database, hospitalized patients had to have received 4 or more ABLC doses for treatment of a fungal infection. Participating clinicians performed a retrospective review of each patient's hospital chart, and information was recorded on a standardized data collection form. An outcome assessment was performed at ABLC therapy completion; this was done at discharge if the patient was to continue antifungal therapy after hospitalization.

The participating clinician was instructed to choose 1 of 3 categories that best described the patient's status at the beginning of ABLC therapy:

- Patient received first-line ABLC therapy.
- Patient received second-line ABLC therapy.
- Patient had preexisting renal disease.

Patients who received second-line ABLC therapy were further classified either as being intolerant of prior antifungal therapy or as having disease refractory to prior antifungal therapy. "Intolerant," "refractory," and "preexisting renal disease" were defined by the participating clinician; the CLEAR database did not define these terms. Clinical outcome was also defined by the participating clinician and categorized as cure, improvement, stable disease, deterioro-

Table 1 – Characteristics of 64 zygomycosis patients*

Characteristic	Number of patients with zygomycosis (%)
Patient status at start of ABLC therapy	
First-line therapy	10 (16)
Second-line therapy	
Refractory to prior antifungal therapy	23 (36)
Intolerant of prior antifungal therapy	12 (19)
Preexisting renal disease	
Unknown	1 (2)
Underlying medical condition†	
Diabetes	18
Leukemia	17
Solid organ transplantation	10
Bone marrow transplantation	8
AIDS	6
Solid tumor	5
Site of infection‡	
Sinus cavities	32
Lungs	22
Skin	9
CNS	9
Bone	6
Oropharynx	5
Blood	2
Peritoneum/ascites	2
Esophagus	1
Liver	1
Kidney	1
Other	12

ABLC, amphotericin B lipid complex.

*Median age, 45 years (range, 10 - 77 years).

†Patients may have had more than 1 underlying condition.

‡Patients may have had more than 1 site of infection.

Table 2 – End-of-therapy clinical efficacy by patient status at start of ABLC therapy

Patient status	Clinical result (number of responders)					Total	Response rate (%)
	Cured	Improved	Stable	Deteriorated	Indeterminate		
First-line therapy	2	2	4	2	0	10	8/10 (80)
Second-line therapy							
Refractory to prior antifungal therapy	2	9	4	7	1	23	15/23 (65)
Intolerant of prior antifungal therapy	3	4	2	2	1	12	9/12 (75)
Preexisting renal disease	1	10	3	2	2	18	14/18 (78)
Unknown	0	0	0	1	0	1	0/1 (0)
Total (%)	8 (13)	25 (39)	13 (20)	14 (22)	4 (6)	64	46/64 (72)

ABLC, amphotericin B lipid complex.

ration, or undetermined status. Patients judged to be cured, improved, or stable at the end of therapy were considered ABLC responders. Information about the use of surgical debridement as primary or adjuvant treatment was not collected.

The average daily dose (mg/kg/d) of ABLC was calculated by dividing the total dose of ABLC administered by the patient's weight and the number of days from the first to the last dose of therapy during hospitalization. The duration of therapy was calculated as the number of days from the first to the last day of ABLC therapy. Patients' serum creatinine values were noted at the beginning and at the end of therapy. Information on previous and concomitant medication use, including the use of amphotericin B, fluconazole, cyclosporine, tacrolimus, and antibiotics, was also collected.

Results

The CLEAR database search yielded a total of 64 patients with zygomycosis. Table 1 shows patient characteristics. Underlying conditions included diabetes (n = 18), leukemia

(n = 17), solid organ transplantation (n = 10), bone marrow transplantation (n = 8), AIDS (n = 6), and solid tumors (n = 5). Patients may have had more than 1 underlying condition. The most common sites of infection were the sinus cavities, lungs, skin, and CNS. Patients may have had multiple sites of infection; for

Overall clinical response to ABLC therapy for all underlying conditions was 72%.

example, 6 patients had both sinus and CNS involvement, and 3 patients had both sinus and lung involvement.

The median age of all patients was 45 years (range, 10 to 77 years). The median daily ABLC dose was 4.82 mg/kg (range, 0.9 to 12.6 mg/kg), and the median duration of therapy was 16 days (range, 5 to 180 days).

All but 1 of the 64 patients were

categorized as having received first- or second-line ABLC therapy or having had preexisting renal disease. Ten patients (16%) received first-line therapy, 35 patients (55%) received second-line therapy, and 18 patients (28%) had preexisting renal disease. Of the 35 patients who received second-line therapy, 12 (34%) were intolerant of prior antifungal therapy and 23 (66%) had disease that was refractory to prior antifungal therapy.

Of the 57 patients identified as recipients of prior medications, 39 (68%) had received amphotericin B and 13 (23%) had received fluconazole. Many patients had received multiple prior medications. Of the 39 patients who had received prior amphotericin B, 17 were categorized as having disease refractory to prior antifungal therapy, 12 as being intolerant of prior antifungal therapy, and 7 as having preexisting renal disease; the status of the remaining 3 patients was unknown. Of the 13 patients who had received prior fluconazole, 7 were categorized as having disease refractory to prior antifungal therapy, 1 as being intolerant of prior antifungal therapy, and 3 as having

preexisting renal disease; the status of the remaining 2 patients was unknown.

Overall clinical response to ABLC therapy for all underlying conditions was 72% (Table 2). Eight (80%) of 10 patients who received ABLC as first-line therapy responded to ABLC. Of patients who received second-line ABLC therapy, 15 (65%) of 23 patients with disease refractory to prior antifungal therapy and 9 (75%) of 12 patients intolerant of prior antifungal therapy responded. Fourteen (78%) of 18 patients with preexisting renal disease responded to ABLC therapy.

Table 3 illustrates the response rates by site of infection. Of 45 patients with disseminated zygomycosis, 6 were cured, 16 experienced disease improvement, and 7 had stable disease at the end of ABLC therapy, resulting in an overall response rate of 64%. Patients with sinus infections had a 92% response rate (12 of 13 patients); those with lung infections had a 67% response rate (2 of 3); and those with oropharyngeal and liver infections had a 100% response rate.

At the end of ABLC treatment, 1 blood and 38 tissue specimens were mycologically tested, with 11 specimens (28%) showing eradication of *Zygomycetes* organisms. Mycologic eradication occurred in the blood

specimen; 2 (67%) of 3 bone specimens; 4 (25%) of 16 lung specimens; 1 (50%) of 2 skin specimens; 1 (33%) of 3 other specimens; and 2 (40%) of 5 unidentified specimens.

Of 18 patients with preexisting renal disease, 14 had a median change in baseline to end-of-therapy serum creatinine values of 1 mg/dL or less. Of the 4 patients with a median change in baseline to end-of-therapy serum creatinine values of greater than 1 mg/dL, 1 had an un-

derlying solid tumor and 3 had undergone solid organ transplantation. One of the solid organ recipients experienced a decrease in the serum creatinine level by the end of therapy; the remaining 3 patients experienced an increase in the serum creatinine level by the end of therapy. The duration of ABLC therapy for the solid tumor patient and 2 solid organ recipients who experienced increases in serum creatinine levels were 10, 14, and 20 days, respectively, whereas the solid organ recipient who experienced a decrease in serum creatinine level received ABLC for 20 days. Two of the 3 patients who experienced an increase in serum creatinine levels received concomitant tacrolimus or vancomycin, and the solid organ recipient who experienced a decrease in serum creatinine levels received cyclosporine concomitantly.

Discussion

Effective management of underlying comorbid conditions, surgical debridement, and amphotericin B have been the mainstays of zygomycosis treatment. However, amphotericin B–induced nephrotoxicity poses a significant obstacle to optimal treatment. The availability of ABLC within the past few years has provided an attractive alternative for the management of zygomycosis. This lipid formulation of amphotericin B was developed to preserve the broad spectrum and fungicidal activity of conventional amphotericin B while minimizing its nephrotoxicity.

A comparison of area under the curve and clearance values, which estimate the rate of drug distribution into the tissues, after ABLC and conventional amphotericin B administration suggests that ABLC is more rapidly distributed to the tis-

Despite the high cumulative ABLC doses administered to patients in this study, renal tolerance was evident.

derlying solid tumor and 3 had undergone solid organ transplantation. One of the solid organ recipients experienced a decrease in the serum creatinine level by the end of therapy; the remaining 3 patients experienced an increase in the serum creatinine level by the end of therapy. The duration of ABLC therapy for the solid tumor patient and 2 solid organ recipients who experienced increases in serum creatinine levels were 10, 14, and 20 days, respective-

Table 3 – End-of-therapy clinical efficacy by site of infection

Site of infection	Clinical result (number of responders)					Total	Response rate (%)
	Cured	Improved	Stable	Deteriorated	Indeterminate		
Disseminated	6	16	7	13	3	45	29/45 (64)
Liver	0	0	1	0	0	1	1/1 (100)
Lungs	1	1	0	1	0	3	2/3 (67)
Oropharynx	0	1	1	0	0	2	2/2 (100)
Sinus	1	7	4	0	1	13	12/13 (92)
Total (%)	8 (13)	25 (39)	13 (20)	14 (22)	4 (6)	64	46/64 (72)

sues, where it exerts its antifungal effect.¹¹⁻¹³ The longer plasma half-life of ABLC and lower percentage of the dose excreted during the first 24 hours compared with conventional amphotericin B may help explain the lower incidence of nephrotoxicity reported with ABLC, because less drug is being delivered to the kidneys for excretion.¹⁴ Despite the high cumulative ABLC doses administered to patients in this study, renal tolerance was evident, even among patients with preexisting renal disease or those at high risk for having renal disease develop, such as patients with diabetes.

The data collected from the CLEAR database show that ABLC is effective therapy for zygomycosis, even among patients with known underlying renal disease or at high risk for renal toxicity. Response to therapy was particularly strong in patients who had received no prior antifungal therapy, suggesting that ABLC should be considered for use as a first-line therapy in patients with zygomycosis. Analyses of these data indicate that serum creatinine levels remained stable during ABLC therapy, even with concomitant administration of drugs known to be nephrotoxic, such as cyclosporine, tacrolimus, the aminoglycosides, and vancomycin.

In the CLEAR database, 63 of 64 patients were categorized as receiving first- or second-line ABLC therapy or having preexisting renal disease. Although the CLEAR database did not define "refractory," "intolerant," and "underlying renal disease," the majority of patients were categorized by the participating clinician as intolerant of or having disease refractory to conventional amphotericin B, and the majority of patients with underlying renal disease did not receive prior amphotericin B or fluconazole therapy.

Results of the largest study evalu-

ating second-line ABLC therapy for invasive fungal infections (N = 556) reported an overall response rate of 71% (17 of 24 patients) in zygomycosis patients.¹⁵ In patients with pulmonary zygomycosis (n = 14), disseminated zygomycosis (n = 1), sinus zygomycosis (n = 6), and single-organ extrapulmonary zygomycosis (n = 3), response rates were 71%, 100%, 67%, and 67%, respectively. In all 556 patients, the mean serum creatinine values gradually decreased, reaching statistically significant reductions by the third week of ABLC therapy. Patients with preexisting renal disease (ie, serum creatinine value of 2.5 mg/dL or greater) also experienced a reduction in mean serum creatinine values during ABLC therapy.

In 3 open-label studies, 67 assessable solid organ transplant recipients with invasive fungal infections (6 with zygomycosis) received ABLC therapy.¹⁶ Overall, 39 (58%) of the patients had a complete response, and 3 (50%) of 6 zygomycosis patients had a complete response (defined as a resolution of all attributable pretreatment signs and symptoms of invasive mycosis at the end of treatment). The mean baseline serum creatinine level in all patients was 3.2 mg/dL, and 81% had stable or improved renal function at the end of treatment.

Published case studies have also shown promising results with ABLC therapy. Examples include a diabetic patient with rhinocerebral zygomycosis who was able to tolerate high doses of ABLC despite impaired renal function¹⁷; a patient with AIDS and isolated renal zygomycosis who tolerated ABLC and achieved complete remission for 18 months¹⁸; a neutropenic patient with disseminated zygomycosis in whom ABLC reversed the nephrotoxicity that had occurred with conventional amphotericin B¹⁹; and a diabetic patient

whose rhinocerebral zygomycosis was cured with ABLC therapy.²

Reports of successful outcomes of ABLC therapy for other difficult-to-treat fungal infections, such as aspergillosis and cryptococcal meningitis, support the use of ABLC as a safe and effective alternative to amphotericin B.²⁰⁻²²

Collectively, the results of the CLEAR database analysis and other studies and case reports support the safety and efficacy of ABLC therapy for zygomycosis. In the CLEAR database analysis, response rates were generally higher in patients who received first-line ABLC therapy than in patients who received second-line ABLC therapy, and most patients with preexisting renal disease were able to tolerate ABLC without further deterioration in renal function. ABLC should be considered for first-line therapy in patients with zygomycosis, especially in patients with preexisting renal disease or those who are at high risk for having renal disease develop. ❖

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