

Phase I Evaluation of the Safety and Pharmacokinetics of Murine-Derived Anticryptococcal Antibody 18B7 in Subjects with Treated Cryptococcal Meningitis

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A promising approach to improving outcomes in patients with cryptococcal meningitis is to use adjunctive passive immunotherapy with a monoclonal antibody (MAb) directed against the capsular polysaccharide of *Cryptococcus neoformans*. This is the first application of MAb therapy for the treatment of a fungal disease in humans. We determined the safety and maximum tolerated dose of the murine anticryptococcal MAb 18B7 in a phase I dose-escalation study. The subjects were human immunodeficiency virus-infected patients who had been successfully treated for cryptococcal meningitis. Six dosing cohorts received MAb 18B7 at 0.01 to 2 mg/kg of body weight as a single infusion. Three patients each received 0.01, 0.05, 0.2, and 0.5 mg of MAb 18B7 per kg without significant adverse events. Four of the subjects who received the 1-mg/kg dose had mild study drug-associated toxicity, including transient nausea, vomiting, back pain, and urticarial rash. Two of the subjects who received 2 mg/kg developed drug-associated mild to moderate nausea, vomiting, chills, and myalgias. One of the subjects who received 2 mg/kg developed intracranial hypertension 10 weeks after MAb 18B7 administration. Serum cryptococcal antigen titers in the cohorts receiving doses of 1 and 2 mg/kg declined by a median of twofold at 1 week and a median of threefold at 2 weeks postinfusion, but the titers subsequently returned toward the baseline values by week 12. The half-life of MAb 18B7 in serum was approximately 53 h, while the MAb was undetectable in the cerebrospinal fluid of all patients. These data support the continued investigation of MAb 18B7 at a maximum single dose of 1.0 mg/kg.

There has been little progress in the treatment of cryptococcal meningitis since the introduction of fluconazole in 1990. When individuals with AIDS and meningeal cryptococcosis are treated with either amphotericin B or fluconazole alone, only 40 to 50% have sterile cerebrospinal fluid (CSF) after 2 weeks (1, 2, 26, 48). Although the combination of either amphotericin B or fluconazole with flucytosine results in a modest improvement in treatment success, more than 25% of subjects fail therapy (1, 25, 26, 33, 50). Furthermore, the neurological sequelae of cryptococcal meningitis remain a distressingly common cause of decreased quality of life.

The vast majority of patients with cryptococcal meningitis are immunocompromised. Therefore, a logical approach to the improvement of treatment outcomes in patients with cryptococcosis is to enhance the host immune response to *Cryptococcus neoformans*. One method of enhancing the host response is by the administration of antibodies that bind to *C. neoformans* polysaccharide. In animal models and in vitro studies, antibodies have been shown to enhance opsonization of the organisms, thereby increasing the number of organisms killed (27, 40, 42). The administration of antibodies that bind to cryptococcal polysaccharide has also been shown to promote the clearance of polysaccharide antigen from the serum of experimental an-

imals and humans (13, 14, 41). This enhanced clearance of antigen may be therapeutic, because the capsular polysaccharide of *C. neoformans* has been shown to have multiple immunosuppressive effects. For example, capsular polysaccharide can (i) predispose vaccinated mice to earlier death (30), (ii) cause the phenomenon of antibody unresponsiveness to cryptococcal antigen (CrAg) (43), (iii) inhibit leukocyte migration (6, 51), (iv) enhance human immunodeficiency virus (HIV) infection in vitro (44, 45), (v) induce shedding of L-selectin (7), (vi) promote cerebral edema (18–21), (vii) induce T lymphocytes to secrete immunosuppressive molecules (3), (viii) promote dysregulation in cytokine production (46, 52, 53), and (ix) inhibit phagocytosis (24). For all of these reasons, the capsular polysaccharide of *C. neoformans* is a major virulence factor that interferes with host defense mechanisms from clearing this organism from the bloodstream and infected tissues.

Administration of antibodies directed against *C. neoformans* capsular polysaccharide to infected mice has prolonged survival (9, 16, 35, 37, 38), reduced the tissue fungal burden, and enhanced granuloma formation (10). Also, antibodies to capsular polysaccharide enhanced the killing of *C. neoformans* by amphotericin B (8, 15, 39), fluconazole (36), and flucytosine (11) in mice and by isolated leukocytes in vitro (34).

On the basis of these promising preliminary data, we carried out a phase I, multi-institution, open-label, nonrandomized, dose-escalation study of a murine-derived anticryptococcal antibody (monoclonal antibody [MAb] 18B7) in HIV-infected

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subjects who had been successfully treated for cryptococcal meningitis. This is the first application of MAb therapy for the treatment of a fungal disease in humans. The trial was designed to determine the maximum tolerated dose of MAb 18B7 and to assess the impact of a single dose of this antibody on the serum and CSF CrAg titers.

MATERIALS AND METHODS

Study subjects met the following inclusion characteristics: (i) they were HIV infected and >18 years of age; (ii) they had a history of culture-proven cryptococcal meningitis; (iii) they had successfully completed at least 6 weeks of therapy for cryptococcal meningitis, with resolution of all signs and symptoms of cryptococcal meningitis; and (iv) they had a negative posttreatment CSF culture for *C. neoformans*, or if no posttreatment CSF culture was available, they must have been asymptomatic for at least 12 weeks prior to enrollment. Additionally, the subjects were required to have a serum CrAg level of >1:16 and to be on a stable antiretroviral regimen for more than 4 weeks prior to study entry. Exclusion criteria included (i) a history of treatment with any murine-derived materials, (ii) participation in another study protocol precluding the use of an experimental agent, (iii) evidence of another active opportunistic infection, or (iv) the use of systemic glucocorticoid therapy or therapy with other immunomodulating agents within 30 days of study entry. We chose this study population because the anticipated target population for treatment with this agent would be those with active cryptococcal disease, of whom greater than 90% would have HIV infection. Furthermore, we wished to evaluate the effect that the MAb would have on the clearance of CrAg, yet we did not want to confound this assessment in the setting of active infection, when there would be continued production of CrAg. A population of subjects without cryptococcal antigenemia was not used because assessments of the pharmacokinetics (PKs) of the anticryptococcal MAb in such a population is of very limited interest; sensitization of such subjects to murine products seemed unwise, as multiple agents derived from murine products have entered the commercial arena; and the PKs of the antibody were unlikely to mirror those in the target population because no antigen-antibody complexes that would presumably alter the kinetics of the anticryptococcal antibody would be created.

The study agent was manufactured at the Massachusetts Public Health Biologic Laboratories (Boston, Mass.) and stored at and distributed to the study sites by the National Institutes of Health Division of Microbiology and Infectious Diseases Clinical Agents Repository in Rockville, Md.

Six escalating-dose cohorts with three study subjects per cohort were examined to determine the maximum tolerated dose of MAb 18B7. The six doses were 0.01, 0.05, 0.2, 0.5, 1.0, and 2.0 mg of MAb 18B7 per kg of body weight; and the doses were infused intravenously over 2 h with direct observation and monitoring of vital signs. The maximum tolerated dose was exceeded if more than one subject among the first three subjects or two subjects among an expanded cohort of six subjects developed a possible, probable, or definite study-related serious adverse event (SAE). An SAE was defined as a grade 3, grade 4, or lethal adverse event according to the Table for Grading Adult Adverse Experiences in the Division of AIDS *Serious Adverse Event Reference Manual* (5a).

A response to the antibody infusion was inferred from changes in serum CrAg titers, which were measured at the baseline, at 4 and 24 h, and then at 7, 14, 28, 56, and 70 days after the MAb 18B7 infusion. Serum was assayed for the MAb 18B7 concentration at 5 min before the initiation of the infusion; at 15, 30, and 60 min and 2 h into the infusion; at 4, 6, 8, and 12 h after the start of the infusion; and on days 7, 14, 28, 56, and 70 after the infusion. Lumbar puncture for CSF collection was performed 4 to 6 h after the initiation of MAb 18B7 infusion for CrAg titer and antibody measurement. The samples were tested for the presence of human anti-mouse antibodies (HAMAs) at the baseline and at days 7, 14, 28, 56, and 70.

The CrAg titer was measured by a latex agglutination assay (Immuno-Mycolitics, Inc., Norman, Okla.). Serum and CSF specimens were sent overnight to the central laboratory on wet ice, and titers were measured within 24 to 48 h of collection. Samples were then placed in batches and stored frozen at -70°C until they were thawed and the titers were measured at the conclusion of study by latex agglutination assay and enzyme-linked immunosorbent assay (Meridian, Cincinnati, Ohio). The MAb 18B7 and HAMA levels were measured by radioimmunoassays (I^{125}) at the central laboratory at the conclusion of the study (22, 23). Quantitative HIV RNA assays were performed at the central laboratory, while CD4 and CD8 lymphocyte counts were measured at each site.

The peak concentration in serum (C_{max}), the C_{max} per unit dose ($C_{\text{max}}/\text{dose}$, which is equal to $C_{\text{max}}/\text{infusion dose}$), and the time to C_{max} (T_{max}) of MAb 18B7 were determined by visual inspection of the data. The observed first half-life ($t_{1/2\text{obs}}$; i.e., the time required for C_{max} to decay to half of its value) was deter-

TABLE 1. HIV loads

Dosing cohort	Subject no.	HIV load (\log_{10})				
		Baseline	Day 1	Day 7	Day 14	Day 84
10 $\mu\text{g}/\text{kg}$	001	0.00	0.00	0.00	0.00	0.00
	002	1.91	1.91	0.00	2.13	2.71
	003	1.90	2.11	1.91	2.25	1.92
50 $\mu\text{g}/\text{kg}$	004	2.57	2.38	2.70	2.40	3.77
	005	3.94	4.38	4.09	4.18	4.27
	006	3.71	3.66	NT ^a	NT	5.60
200 $\mu\text{g}/\text{kg}$	007	4.24	4.34	3.93	4.02	4.19
	008	4.33	4.41	4.35	4.66	4.83
	009	0.00	0.00	0.00	0.00	0.00
500 $\mu\text{g}/\text{kg}$	010	3.15	3.07	3.20	2.91	1.99
	011	0.00	0.00	0.00	0.00	0.00
	012	3.54	3.57	3.83	3.58	4.07
1.0 mg/kg	013	4.07	5.02	4.60	5.03	4.68
	014	4.06	3.99	4.53	4.53	5.28
	015	0.00	0.00	0.00	0.00	2.50
	020	2.98	3.10	2.45	1.98	0.00
2.0 mg/kg	016	2.67	2.60	NT	2.61	0.00
	017	3.51	NT	3.59	— ^b	—
	018	1.76	0.00	2.63	1.86	0.00
	019	0.00	0.00	0.00	NT	0.00

^a NT, not tested.

^b —, the subject died.

mined by log-linear interpolation. The area under the curve (AUC) of the MAb 18B7 concentration-over-time plot for each patient was calculated by using the trapezoidal rule during the infusion portion of the curve and the log-linear trapezoidal rule during the exponential decay (postinfusion) portion of the curve (4). If the last concentration measured was greater than 0, then the AUC from the last measured concentration through infinity was estimated by integration as C_{final}/β , where C_{final} is the final measured concentration and β is the terminal first-order elimination rate constant (12). β was estimated by using the negative semilogarithmic slope (i.e., negative change in the log concentration/change in time) by using the last two observed MAb 18B7 concentrations. When reasonable estimates of β could not be made due to noise at concentrations close to 0, then the final concentration was assumed to be equal to 0 and the final segment of the AUC was calculated by using the trapezoidal rule. AUC was normalized for the infusion dose by $\text{AUC}/\text{dose} = \text{AUC}/\text{infusion dose}$.

Clearance (CL), mean residence time (MRT), and volume of distribution at steady state (V_{ss}) were calculated by use of the standard formulae (22). Spearman rank correlations were performed to test whether each of the noncompartmental PK parameters was independent of the infusion dose. Spearman rank correlations were also performed to test for any associations between the MAb 18B7 concentrations (as C_{max} and AUC) and the minimum CrAg concentration or the minimum CrAg concentration as a percentage of the baseline concentration.

This study was approved by the institutional review board of each medical center and was conducted at the respective general clinical research centers. The study was approved and conducted by members of the National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group and was monitored by an independent safety monitoring committee administered by the Division of Microbiology and Infectious Diseases, NIAID.

RESULTS

Twenty HIV-positive subjects were enrolled in the study; 18 were male, the median age was 39 years, 8 were white, 8 were black, and 4 were Hispanic. The serum CrAg titers ranged from 1:4 to 1:8,192. All subjects were CSF culture negative at the baseline. The median CD4 lymphocyte level at the baseline was 103 cells/mm³ (range, 33 to 322 cells/mm³). Nineteen (95%) subjects were monitored for 84 days; one subject died during the study period, but the death was not related to the study ther-

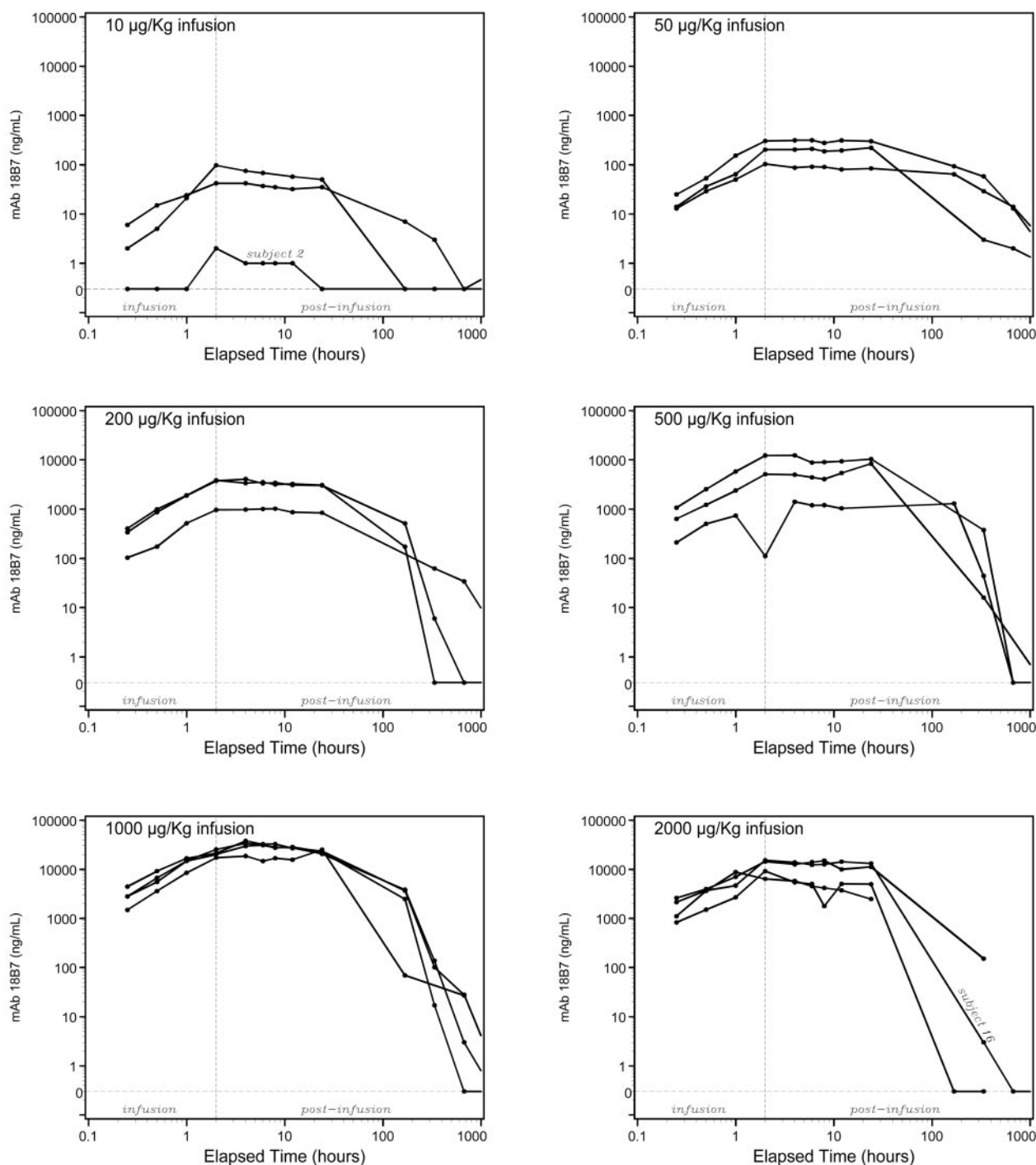


FIG. 1. MAb 18B7 concentrations in individual subjects over time grouped by infusion dose. The vertical dashed reference lines at 2 h indicate the end of the MAb infusion. All of the data for subject 2 and the data for subject 16 after 14 days (336 h) were excluded from the PK analyses due to high levels of HAMA.

apy. Changes in HIV infection status, e.g., changes in $CD4^+$ T-lymphocyte counts, were not observed. However, HIV loads increased by 0.5 \log_{10} in 7 of the 20 subjects, including 3 of 4 subjects in the cohort that received 1.0 mg of the study drug per kg (Table 1).

Adverse events were common among the study subjects, with 16 (80%) of the 20 subjects experiencing some adverse

event during the study period. Six (30%) subjects experienced SAEs; however, in only one was the SAE believed to be due to MAb 18B7. One subject died during the follow-up period due to septic and thrombotic complications associated with a central venous catheter, and this adverse event was not related to the study drug. MAb 18B7 was well tolerated. When MAb 18B7 was given at 1.0 mg/kg, immediate infusion-related my-

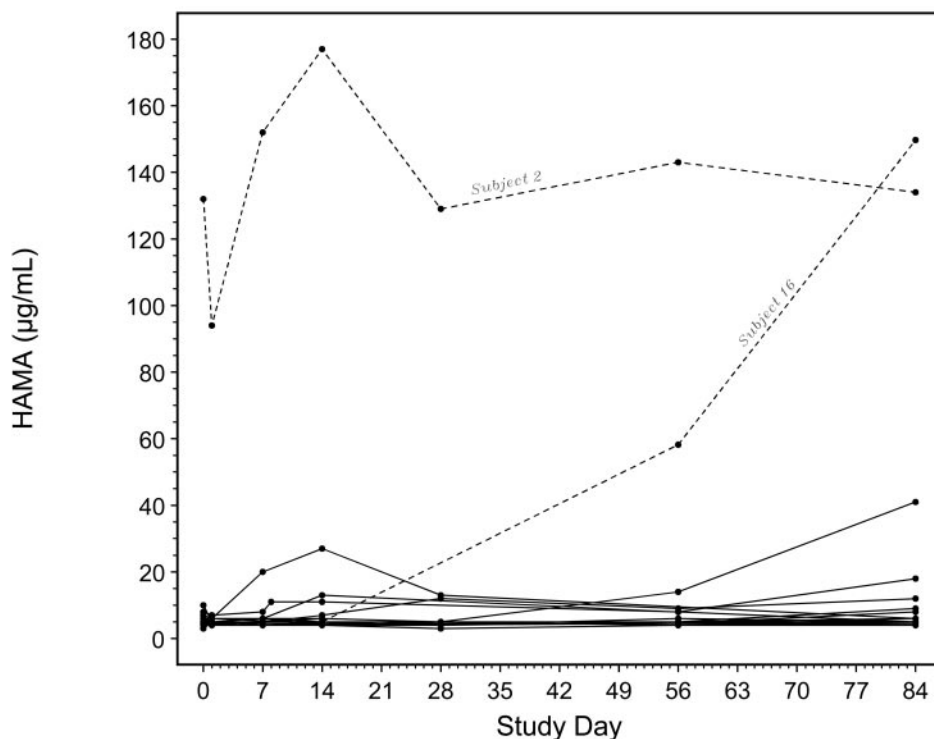


FIG. 2. HAMA concentrations in individual subjects over time. HAMA concentrations for the same individual are connected, and those for subjects 2 and 16 are connected with dashed lines.

algias and back pain were observed in two subjects. In addition, at a dose of 1.0 mg/kg, a single subject developed a transient urticarial rash at day 7. Mild infusion-related nausea associated with vomiting was also observed at the 1.0-mg/kg dosing level. At the 2.0-mg/kg dose, two of four subjects developed notable infusion-associated back and muscle pain, with one of these subjects (subject 19) also developing nausea, retching, and hematemesis, which resulted in a significant decline in the subject's hemoglobin level. The same subject subsequently developed severe intracranial hypertension 71 days after antibody infusion. The lumbar and cisternal CSF samples were negative for CrAg, and serum and CSF were negative for MAb 18B7. A ventricular CSF sample obtained 2 weeks later at the time of ventriculoperitoneal shunting had a ventricular CrAg titer of 1:8. All CSF cultures were negative. CD4⁺ T-lymphocyte counts were declining. This episode of intracranial hypertension was thought to be a culture-negative relapse of cryptococcal ventriculitis, but an association with MAb 18B7 administration could not be conclusively excluded. With this second SAE, the independent data safety monitoring committee deemed the 2.0-mg/kg dosing level to have exceeded the predefined maximum tolerated dose criteria.

Data for one subject receiving the 0.01-mg/kg infusion dose were excluded from the PK analysis due to high HAMA levels found prior to study drug infusion that persisted throughout the study period. MAb 18B7 titers for another subject collected after 14 days (336 h) were not used due to high HAMA concentrations.

T_{max} s ranged from 1 to 24 h, with 2 h (the end of infusion) being the most frequent T_{max} (6 of 19 subjects; Fig. 1). Data for subjects 2 and 16 were excluded from the noncompartmental

analyses due to the possible influence of their high HAMA levels (Fig. 2). All values for all concentrations for samples obtained after 24 h were missing for subject 19, and thus, the data for this subject were excluded from the calculations of AUC and AUC-derived parameters (CL, MRT, and V_{ss}) to avoid potential bias from the extensive extrapolation of the AUC from 24 h to infinity for this subject. The medians and ranges of the parameter estimates from the noncompartmental PK analysis with their ranges are listed in Table 2. Fifty-three hours was required for MAb 18B7 concentrations to decrease from their C_{max} by half ($t_{1/2obs}$). This $t_{1/2obs}$ decreased as the infusion dose increased (Spearman rank correlation [r] = -0.51; P = 0.02). The MRT for MAb 18B7 molecules within the body was estimated to be 73 h, giving an MRT-calculated half-life of 51 h. V_{ss} was 4.7 liters, with a median CL of 0.1 liters · h⁻¹. All 20 subjects underwent lumbar puncture within

TABLE 2. MAb 18B7 parameter estimates from noncompartmental PK analysis

Noncompartmental PK parameter ^a	Median value	Range (minimum, maximum)	r^a	P value
$C_{max}/dose$ (liter ⁻¹)	0.12	0.032, 0.52	0.24	0.3309
T_{max} (h) ^b	4	1, 24	0.18	0.4664
$t_{1/2obs}$ (h)	53	17, 214	-0.51	0.0244
AUC/dose (h · liter ⁻¹)	10.4	1.2, 31	-0.063	0.7973
CL (liter · h ⁻¹)	0.096	0.032, 0.85	0.063	0.7973
V_{ss} (liter)	4.7	1.9, 41	-0.10	0.6785
MRT (h)	73	21, 422	-0.42	0.0700

^a r , Spearman rank correlation versus dose.

^b The mode was 2 h (6 of 19 patients).

TABLE 3. Serum CrAg titers by latex agglutination

Cohort	Subject no.	Log ₂ serum CrAg titer							Minimum % base ^a	Geometric mean ^b
		Baseline	Day 1	Day 7	Day 14	Day 28	Day 56	Day 84		
10 µg/kg	001	12	10	10	10	12	11	10	25	35
	002	10	10	12	12	10	12	12	100	
	003	3	4	4	4	6	9	2	50	
20 µg/kg	004	12	11	12	12	12	12	10	25	40
	005	6	7	7	7	9	7	ND ^c	200	
	006	11	12	ND	ND	8	10	10	12.5	
200 µg/kg	007	2	0	0	0	0	1	LE ^d	50	10
	008	8	LE	LE	7	6	6	3	3.1	
	009	13	14	14	12	14	10	9	6.3	
500 µg/kg	010	13	14	13	14	13	14	12	50	25
	011	5	3	3	4	5	4	3	25	
	012	10	9	11	9	7	7	8	12.5	
1.0 mg/kg	013	7	7	5	4	5	6	5	12.5	7
	014	5	3	3	1	4	3	5	6.3	
	015	5	4	3	3	3	7	5	25	
	020	7	4	5	1	3	ND	ND	1.6	
2.0 mg/kg	016	6	6	LE	4	4	5	5	25	12
	017	7	ND	ND	6	— ^e	—	—	—	
	018	9	5	7	7	6	5	4	3.1	
	019	11	10	9	8	10	10	10	12.5	

^a Minimum % base, the minimum serum CrAg titer achieved as a percentage of the baseline serum CrAg titer.

^b Geometric mean of the minimum serum CrAg titer as a percentage of the baseline serum CrAg titer.

^c ND, not done.

^d LE, laboratory error.

^e —, the subject died.

6 h of infusion of the study drug, and no MAb 18B7 was detected in the CSF of any subject.

There was little change in baseline serum CrAg titers following infusion of lower doses of MAb 18B7 when these titers were determined in a sequential fashion (i.e., in real time). However, at doses of 1.0 and 2.0 mg/kg, modest changes in sequential measurements of the serum cryptococcal latex agglutination titers were observed, but they tended to return to the baseline measurements by 10 weeks. Minimum postinfusion CrAg titers as a percentage of the baseline concentration and their geometric means by dose group are listed in Table 3. Spearman rank correlations found significant negative correlations for the minimum CrAg titer versus C_{\max} ($r = -0.543$; $P = 0.0198$) and AUC ($r = -0.502$; $P = 0.040$). When Spearman rank correlations were adjusted for the baseline CrAg titer by correlating the minimum CrAg titer as a percentage of the baseline concentration, the correlations with C_{\max} ($r = -0.393$; $P = 0.1072$) and AUC ($r = -0.340$; $P = 0.1818$) were not significant, although the C_{\max} correlation with a P value of 0.1072 does not exclude the possibility of an association.

At the conclusion of the study, assays for CrAg titers were performed with batched serum specimens that had been frozen at -70°C . The CrAg titers in these serum samples were considerably lower than those obtained in samples tested previously, and subsequent analysis has revealed a significant decline in measurable serum CrAg levels with time (A. Casadevall, personal communication). Finally, the CrAg titers in the same batched serum specimens were measured by enzyme-linked immunoabsorption assay, but these results did not cor-

relate well with the CrAg titers determined at the baseline or follow-up evaluations by the standard latex agglutination assay (31).

HAMAs were found in three subjects (Fig. 2). One subject had detectable HAMAs at the baseline, and two other subjects given 0.5 and 2.0 mg of MAb 18B7 per kg, respectively, developed detectable HAMAs at day 56. The HAMA was immunologically active because the subject with detectable HAMA at the baseline had no detectable MAb 18B7 in serum immediately postinfusion or throughout the postinfusion period. In the other two subjects, the level of MAb 18B7 in serum had already fallen below the measurable levels at the time that HAMA was detected.

DISCUSSION

The adjunctive use of antibody therapy in patients with cryptococcosis combines significant promise with considerable challenges. Specific antibody is currently the only reagent that can potentially assist in the removal of cryptococcal polysaccharide with its many untoward immunological effects (51). In animal models of cryptococcal infection, passive antibody administration has been shown to rapidly clear polysaccharide from serum through the formation of antigen-antibody complexes that are deposited in the liver (28). There were two theoretical concerns regarding the safety of antibody therapy for cryptococcosis during the development of the clinical trial design. First, antibody-mediated phagocytosis of *C. neoformans* has been associated with an increase in the level of HIV

expression in monocytic cells, raising concern that antibody therapy could exacerbate HIV infection in patients with AIDS-related cryptococcosis (17). Second, antibody administration to mice with established cryptococcal infection was associated with cardiovascular collapse and death in some strains of mice as a result of the release of platelet-activating factor (29, 49). Experiments with animals revealed that this toxicity was a function of the antibody dose and could be minimized by slow antibody administration. Consequently, the major goal of this study was to establish the safety of antibody administration in patients with cryptococcal antigenemia. To that end, this study was designed to use a cautious dose-escalation regimen beginning with very low doses of antibody. Fortunately, the major concern of cardiovascular collapse documented in murine studies was not observed in the human subjects. However, we did note that 7 of 20 (35%) subjects had a 0.5 log₁₀ increase in HIV load, including 3 of 4 subjects in the 1.0-mg/kg dosing cohort. This may reflect an *in vivo* correlate of the enhanced HIV replication noted in monocytes undergoing antibody-mediated phagocytosis (17). The observed increases in HIV loads were modest, ranging from 0.53 to 2.5 log₁₀. The results suggest that this murine-derived anticryptococcal antibody can safely be given at doses up to 1.0 mg/kg to patients with cryptococcal antigenemia.

The MAb 18B7 used as a study drug is a murine immunoglobulin G1 antibody which had been shown to mediate protection in mouse models of experimental infection (5). The antibody binds to *C. neoformans* capsular glucuronoxylomannan, which is the primary component of the capsular polysaccharide. Although mouse-human chimeric antibodies have been available for some time, the decision to use a murine MAb was based on persistent uncertainty about the efficacy of the mouse-human chimeric antibodies and concerns regarding possible changes in the specificities of engineered molecules (32). Our observation that about 10% of this patient population developed HAMAs reassures us that host immune responses will not limit the utility of this agent in the majority of the target population, although with repeated dosing, it is probable that HAMAs will evolve more often. However, because HAMA has a relatively late onset, the activity of MAb 18B7 and its effects on the course of cryptococcal meningitis should not be impaired during that critical early period of infection when rapid control of the disease process is essential (47).

The assessment of the pharmacodynamics of MAb 18B7 in humans proved to be difficult and reflects the complex interactions that must occur following infusion of a specific antibody into a host with antigen in both the serum and the tissue compartments. Animal models have shown that antibody binds to antigen in serum and results in rapid uptake by reticuloendothelial cells, which occurs in a background of diffusion of the murine antibody into tissue, antibody binding to tissue antigen, and slow clearance of antibody through normal metabolic mechanisms. Somewhat surprisingly, MAb 18B7 was distributed in a volume that is twice that of plasma. This implies that MAb 18B7 leaves the intravascular space rapidly and is likely bound to tissue-associated antigen. While serum CrAg levels declined following antibody administration, these levels returned toward the baseline values at 12 weeks, probably indicating a large residual reservoir of CrAg. The levels of MAb

18B7 measured and the lack of immunogenicity of the MAb at the doses used support repeated dosing of MAb 18B7, which would lead to higher levels and possibly more rapid and lasting effects on CrAg.

In summary, antibody therapy for cryptococcal meningitis was well tolerated up to doses of 1 mg/kg without evidence of the types of toxicity that were suggested by *in vitro* or animal studies. At the higher antibody doses, we observed evidence of a pharmacological effect, as demonstrated by a reduction in the serum CrAg titers. These results are sufficiently promising to justify continued development of this approach for the management of fungal diseases, particularly cryptococcal meningitis, in which CrAg appears to play such a critical role in the pathophysiology of the disease. Finally, considering the present effort in the historical setting of the development of antimicrobial therapy, we note that this study represents two advances in human therapy: application of MAb therapy to a human mycosis and therapy which intends to mediate a biological effect through the clearance of a microbial antigen.

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