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Mycology | Full-Length Text

Efficacy of an oral lipid nanocrystal formulation of amphotericin B (MAT2203) in the neutropenic mouse model of pulmonary mucormycosis

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ABSTRACT Invasive mucormycosis (IM) is associated with high mortality and morbidity. MAT2203 is an orally administered lipid nanocrystal formulation of amphotericin B, which has been shown to be safe and effective against other fungal infections. We sought to compare the efficacy of MAT2203 to liposomal amphotericin B (LAMB) treatment in a neutropenic mouse model of IM due to *R. arrhizus* var. *delemar* or *Mucor circinelloides f. jenssenii* DI15-131. In *R. arrhizus* var. *delemar*-infected mice, 15 mg/kg of MAT2203 qd was as effective as 10 mg/kg of LAMB in prolonging median survival time vs placebo (13.5 and 16.5 days for MAT2203 and LAMB, respectively, vs 9 days for placebo) and enhancing overall survival vs placebo-treated mice (40% and 45% for MAT2203 and LAMB, respectively, vs 0% for placebo). A higher dose of 45 mg/kg of MAT2203 was not well tolerated by mice and showed no benefit over placebo. Similar results were obtained with mice infected with *M. circinelloides*. Furthermore, while both MAT2203 and LAMB treatment resulted in a significant reduction of ~1.0–2.0log and ~2.0–2.5log in *R. delemar* or *M. circinelloides* lung and brain burden vs placebo mice, respectively, LAMB significantly reduced tissue fungal burden in mice infected with *R. delemar* vs tissues of mice treated with MAT2203. These results support continued investigation and development of MAT2203 as a novel and oral formulation of amphotericin for the treatment of mucormycosis.

KEYWORDS lipid nanocrystal , amphotericin B, MAT2203, liposomal amphotericin B, antifungal agents, *Rhizopus*, *Mucor*, mucormycosis, murine, oral amphotericin B

Diabetic ketoacidosis, neutropenia, and high-dose corticosteroid treatment are all clinical factors that predispose patients to mucormycosis, a life-threatening fungal infection with high mortality rates of >50% (1–3). In the most severe circumstances, patients with brain involvement, persistent neutropenia, and hematogenously disseminated disease have mortality rates >90% (4, 5). Furthermore, COVID-19 (coronavirus disease 2019)-associated mucormycosis has been reported in many countries during the second wave of the COVID-19 pandemic with >50,000 cases reported in India between May and August 2021 (6, 7). Mucorales fungi are the responsible organisms, with *Rhizopus* species being the most common cause of infection worldwide followed by *Mucor* species (8, 9).

There are three drugs used to treat mucormycosis: amphotericin B-based compounds, isavuconazole, and posaconazole. Lipid formulation of amphotericin B [including liposomal amphotericin B (LAMB)] is the first-line therapy for mucormycosis, while the two azoles are reserved for stepdown and/or salvage therapy (10). Although LAMB is less toxic than amphotericin B deoxycholate, considerable toxicity and inability to deliver the drug orally limit its use and contribute to the high mortality seen with mucormycosis.

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A recently developed oral formulation of amphotericin B (MAT2203, Matinas BioPharma) using a proprietary lipid nanocrystal delivery platform has been shown to be safe when given at doses as high as 40 mg/kg and has demonstrated efficacy against murine aspergillosis and murine cryptococcal meningoencephalitis (11, 12), as well as in a human Phase 2 study on cryptococcal meningitis (13). We sought to assess the activity of MAT2203 in our established immunosuppressed murine models of mucormycosis infected by *R. arrhizus* var. *delemar* or *Mucor circinelloides f. jenssenii*. We compared overall survival, median survival time (MST), tissue fungal burden, and histology of target organs to those treated with LAMB.

RESULTS

Susceptibility testing

We determined the minimum inhibitory concentrations (MICs) that resulted in 50% or 90% inhibition of the growth of the fungal spores when compared to no treatment (Table 1). MAT2203 showed 5–10-fold increase in *in vitro* activity against the *R. arrhizus* var. *delemar* and *M. circinelloides* when compared to LAMB.

The *in vivo* activity of MAT2203 against *R. arrhizus* var. *delemar*

Survival

Two survival experiments were conducted to determine the activity of MAT2203 in treating murine mucormycosis due to *R. arrhizus* var. *delemar* 99-880. In the first experiment, neutropenic mice were infected and treated as detailed above. MAT2203 doses of 5 and 15 mg/kg qd showed enhanced overall survival of 20% and 40% when compared to 0% of placebo mice (infection no treatment), respectively. A high dose of 45 mg/kg of MAT2203 did not show benefit over placebo-treated mice. Concordant with previous studies (14, 15), LAMB treatment resulted in a 40% overall survival of mice (Fig. 1A). A repeat study was conducted to confirm the results and to investigate if twice-daily treatment with MAT2203 will result in an enhanced benefit in the survival of mice infected with *R. arrhizus* var. *delemar*. MAT2203 at 15 mg/kg given (qd) and LAMB (10 mg/kg, qd) resulted in a similar protection and an overall survival of immunosuppressed mice of 40% and 50%, respectively (Fig. 1B) ($P = 0.50$). In addition, splitting the daily dose of 15 mg/kg into two doses of 7.5 mg/kg/day (bid) resulted in a similar overall survival of 30% when compared to 15 mg/kg qd dosing. However, treating mice with two doses of 15 mg/kg/day did not protect mice from infection when compared to placebo-treated mice which had 0% survival by day 18 post-infection. Collectively, these results confirm the similar protection afforded by oral MAT2203 when given in doses of 5–15 mg/kg qd to the standard of care of LAMB treatment and that daily doses of MAT2203 at or above 30 mg/kg is not protective.

Because of the concordant results in protection seen with the qd dosing of 15 mg/kg of MAT2203 and 10 mg/kg of LAMB, we combined the data of experiments 1 and 2 and measured the MST for each treatment. The MST was concordant with the overall survival by day 21 post-infection with doses of 5 and 15 mg/kg qd or 7.5 mg/kg of MAT2203 and 10 mg/kg of LAMB showing improved MST of 13, 13.5, 12.5, and 16.5 days, respectively, vs 9 days for placebo-treated mice (Fig. 2). There was no statistical difference between the overall percent survival of mice treated with MAT2203 at 5, 7.5, or 15 mg/kg qd vs LAMB at 10 mg/kg ($P = 0.17$, $P = 0.3$, and $P = 0.6$ for MAT2203 5 mg/kg vs LAMB, MAT2203 7.5 mg/kg vs LAMB, and MAT2203 15 mg/kg vs LAMB, respectively).

TABLE 1 MICs that resulted in 50% and 90% growth inhibition are listed

	R. arrhizus var. *delemar* 99-880		*M. circinelloides f. jenssenii* DI14-131	
Drug	MIC (µg/mL) 50% inhibition	MIC (µg/mL) 90% inhibition	MIC (µg/mL) 50% inhibition	MIC (µg/mL) 90% inhibition
LAMB	0.0156	0.0315	0.0315	0.0625
MAT2203	0.0016	0.0081	0.0039	0.0078

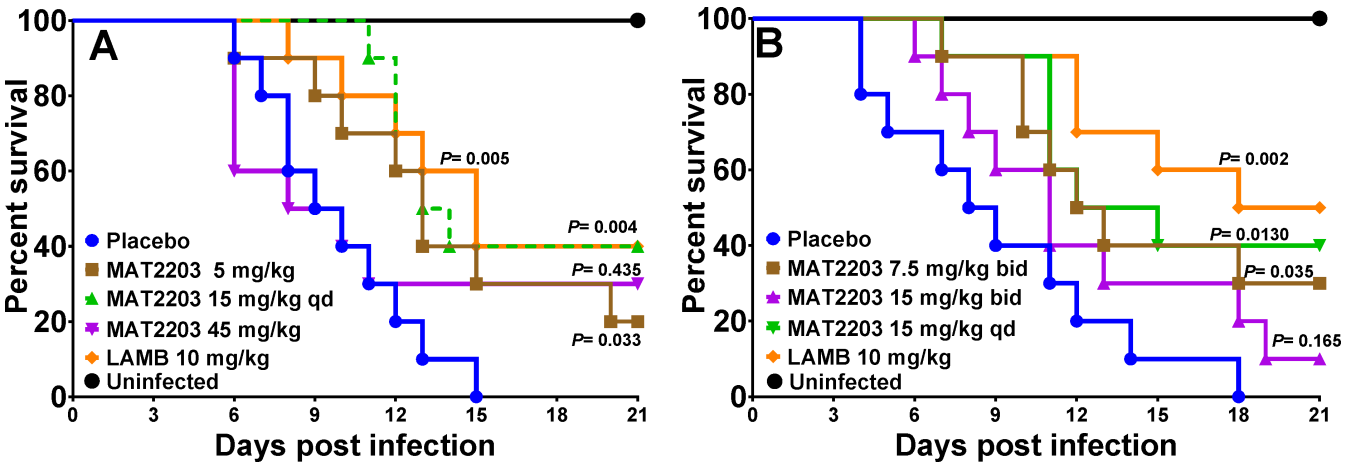
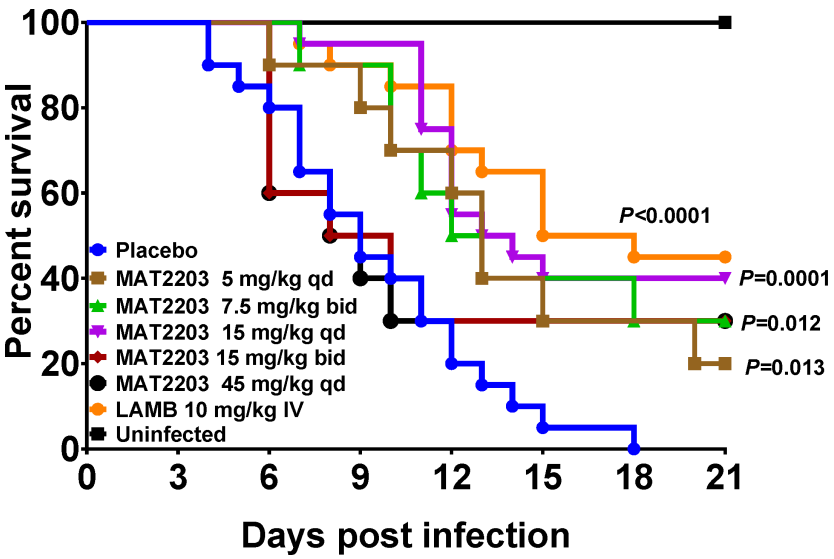


FIG 1 Survival of immunosuppressed mice (n = 10/group) infected with *R. arrhizus* var. *delemar* and treated with either MAT2203 or LAMB. Two independent experiments were conducted [experiment 1 (A) and experiment 2 (B)]. In experiment 1, the delivered infectious inoculum was 1.8×10^4, and in experiment 2, it was 1.5×10^4 spores. Treatment started 16 h post-infection and continued for 7 days for MAT2203 and 4 days for LAMB. *P* values on each of the graphs are vs placebo-treated mice.

Tissue fungal burden

Because MAT2203 enhanced the survival of mice infected with *R. arrhizus* var. *delemar*, we evaluated the effects of this drug on the tissue fungal burden of target organs of the lung and brain (14, 16, 17). Treating mice with 15 mg/kg of MAT2203 qd resulted in ~1.5-log reduction in lung and 1.0-log reduction in brain fungal spores when compared to placebo-treated mice. While a dose of MAT2203 at 5 mg/kg once daily trended to lower fungal burden in the lung, this difference was not significant (Fig. 3). LAMB resulted in ~2.0-log reduction in lung and brain fungal burden vs placebo mice, respectively. LAMB also resulted in a significant reduction in lung and brain tissues of 0.6-log and 0.9-log when compared to 15 mg/kg of MAT2203 (Fig. 3).



Group	MST (days)	% Survival
Placebo	9	0
MAT2203 5 mg/kg qd	13	20
MAT2203 7.5 mg/kg bid	12.5	30
MAT2203 15 mg/kg qd	13.5	40
MAT2203 15 mg/kg bid	9	30
MAT2203 45 mg/kg qd	8.5	30
LAMB 10 mg/kg	16.5	45

FIG 2 Combined data of survival of neutropenic mice infected with *R. arrhizus* var. *delemar* and treated with MAT2203 or LAMB. N = 20 mice per group for placebo, LAMB, MAT2203 (15 mg/kg qd), and N = 10 for uninfected control, MAT2203 (5 and 45 mg/kg qd), and MAT2203 (7.5 and 15 mg/kg bid). *P* values on each of the graphs are vs placebo-treated mice. Data in the table include the median survival times and the overall survival by day 21 post-infection.

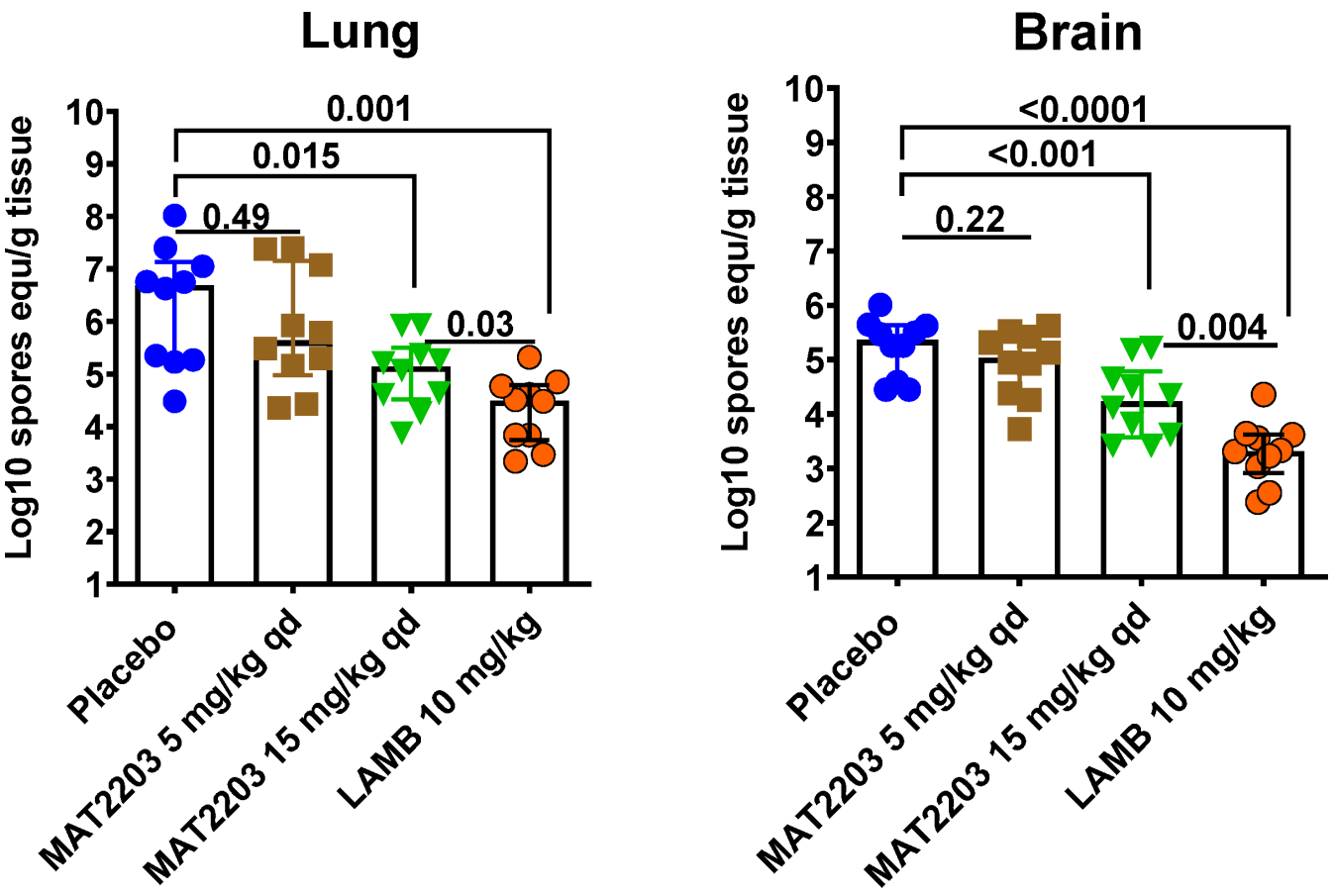


FIG 3 Reduction in tissue fungal burden of immunosuppressed mice infected with *R. arrhizus* var. *delemar*. Mice (n = 10/group) infected intratracheally with *R. arrhizus* var. *delemar* (inhaled inoculum of 2.9×10^4 spores/mouse) and 16 h later treated with MAT2203 5 mg/kg qd or 15 mg/kg qd or with LAMB 10 mg/kg. On day +4, organs were collected and processed for tissue fungal burden by qPCR. Data = median ± interquartile range, and the *y*-axis represents the lower limit of detection. Intergroup *P* values are shown as a dark line. Both MAT2203 at 15 mg/kg and LAMB resulted in a statistically significant reduction in lung and brain fungal burden vs placebo control (Wilcoxon rank sum test).

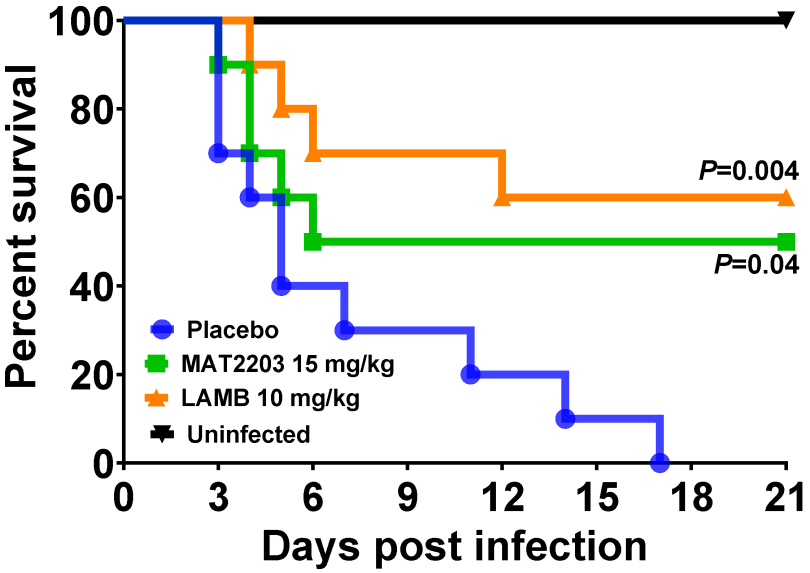
The *in vivo* activity of MAT2203 against *M. circinelloides f. jenssenii*

Survival

To investigate if the protective effect of MAT2203 can be expanded to other Mucorales fungi that are commonly isolated from patients with mucormycosis, we infected immunosuppressed mice with *M. circinelloides f. jenssenii* and 16 h later treated them with either MAT2203 (15 mg/kg qd) or LAMB (10 mg/kg qd) as detailed above. Consistent with the results obtained with mice infected with *R. arrhizus* var. *delemar*, both drugs prolonged median survival time by 13.5 and >21 days for MAT2203 and LAMB, respectively, when compared to 5 days of placebo control. Moreover, both drugs were effective in enhancing overall 21-day survival of 50% for MAT2203-treated and 60% for LAMB-treated mice vs 0% survival for placebo control mice (Fig. 4). The enhancement of overall survival by 15 mg/kg MAT2203 and 10 mg/kg LAMB was comparable (P = 0.42).

Tissue fungal burden and histopathological examination

Because MAT2203 enhanced the survival of mice infected with *M. circinelloides f. jenssenii*, we evaluated the effect of this drug on the tissue fungal burden of target organs of the lung and brain (14, 16, 17). Treating mice with 15 mg/kg of MAT2203 qd resulted in ~2.0-log reduction in the lung and ~1.0-log reduction in the brain fungal burden when



Group	MST (days)	%Survival
Placebo	5	0
MAT2203 15 mg/kg	13.5	50
LAMB 10 mg/kg	>21	60

FIG 4 Survival of neutropenic mice (n = 10/group) infected with *M. circinelloides f. jenssenii* and treated with MAT2203 or LAMB. *P* values on each of the graphs are vs placebo-treated mice. Data in the table include the median survival times and the overall survival by day 21 post-infection.

compared to placebo-treated mice (Fig. 5). Importantly, this reduction in fungal spores was comparable to the reduction seen in mice treated with LAMB.

We also conducted histopathological examination on the same organs processed for the tissue fungal burden experiment. While placebo mice had abscesses full of intact

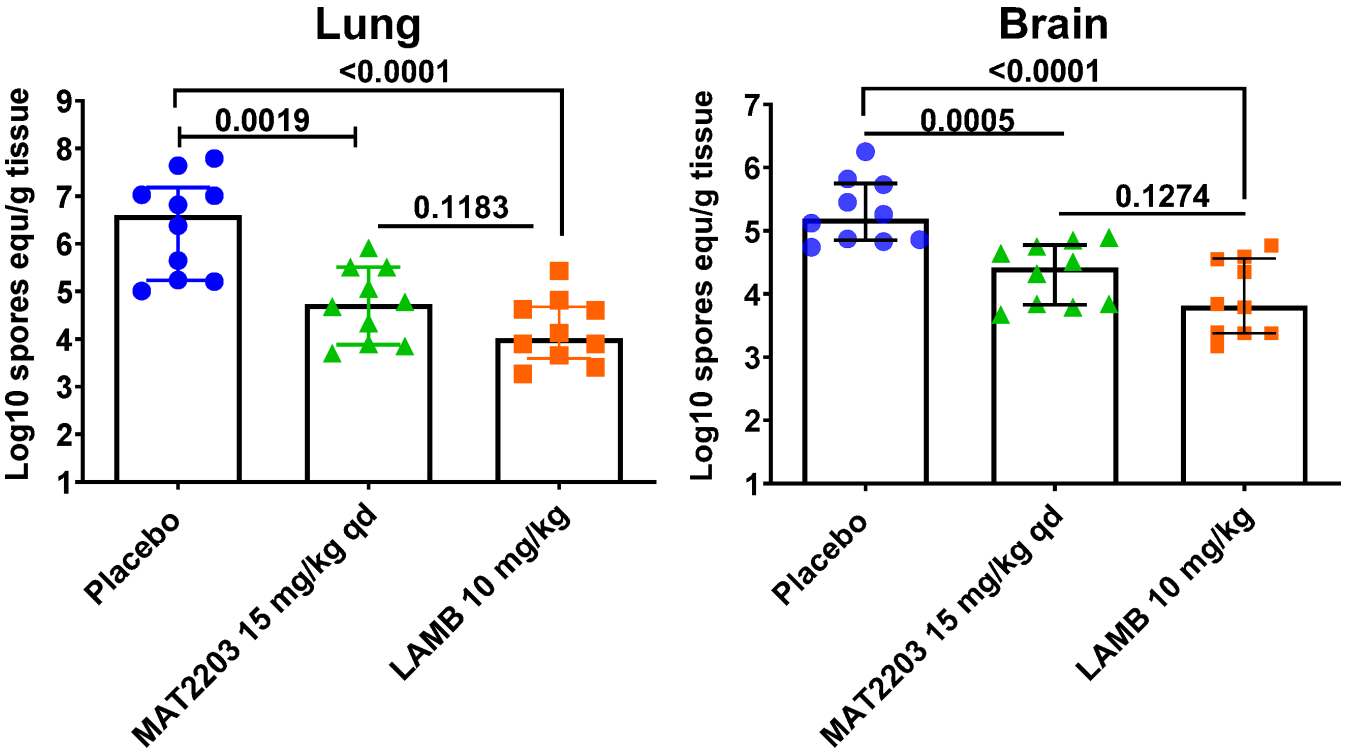


FIG 5 Reduction in tissue fungal burden of neutropenic mice infected with *M. circinelloides f. jenssenii*. Mice (n = 10/group) infected intratracheally with 2.9×10^4 spores/mouse and 16 h later treated with MAT2203 (15 mg/kg qd) or with LAMB (10 mg/kg). On day +4, organs were collected and processed for tissue fungal burden by qPCR. Data = median ± interquartile range, and the *y*-axis represents the lower limit of detection. Intergroup *P* values are shown as a dark line. Both MAT2203 at 15 mg/kg and LAMB resulted in a statistically significant reduction in lung and brain fungal burden vs placebo control (Wilcoxon rank sum test).

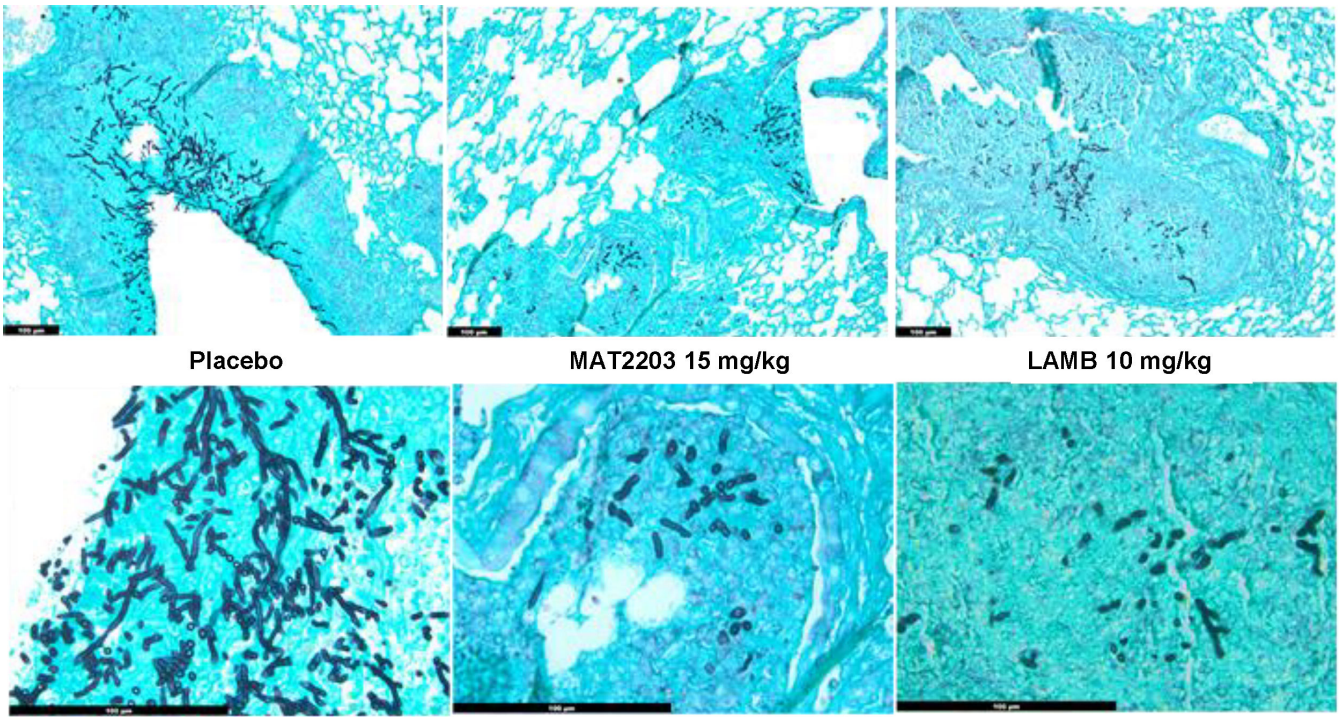


FIG 6 Histology micrographs showing improvement of murine lung infection with MAT2203 or LAMB treatment. Histological examination of lung sections taken from mice infected with *M. circinelloides f. jenssenii* and stained with Grocott methenamine silver revealed fungal pneumonia (indicated the abscesses in the placebo mice with broad aseptate hyphae). While evidence of pneumonia still existed in mice treated with either MAT2203 or LAMB, the number of fungal abscesses was less with shorter and damaged fungal hyphae. Bar is 100 µm.

broad aseptate fungal hyphae [consistent with mucormycosis (18)], mice treated with MAT2203 or LAMB had less fungal abscesses with damaged and shorter hyphae (Fig. 6). Collectively, these results demonstrate similar activity of MAT2203 to the current standard of care of LAMB in most of the conducted experiments.

DISCUSSION

In this study, we have shown that MAT2203 has an *in vitro* killing activity that is 5–10-fold higher than LAMB against two clinical isolates of *R. arrhizus* var. *delemar* and *M. circinelloides f. jenssenii* activity (Table 1). The drug demonstrated *in vivo* efficacy in treating *R. delemar* or *M. circinelloides f. jenssenii* pulmonary infection in immunosuppressed mice. This efficacy is demonstrated by: (i) prolonged median survival time; (ii) enhanced overall survival; (iii) reduced tissue fungal burden of target organs; and (iv) improved histological architecture of infected lungs. Of importance, the MAT2203 activity appeared to be similar in the mouse survival studies to LAMB, while LAMB resulted in significantly improved tissue fungal reduction over MAT2203 when *R. delemar* was the infectious agent.

The 15 mg/kg dose of MAT2203 translates approximately to 0.9 g/day dose for a 60-kg patient. This dose is below the dose level of 1–2 g/day tested in the Phase 1 EnACT trial showing that the drug was well tolerated when given in 4–6 divided daily doses (19). Furthermore, there was no statistical difference in mouse survival between dosing MAT2203 in a single dose of 15 mg/kg or as 7.5 mg/kg bid (Fig. 1B), suggesting that this dose in humans can be divided into two or more doses to ensure maximum benefit. It is prudent to point out that the platform technology used in MAT2203 targets its delivery to the site of infection. However, due to the nature of the drug delivery, a pharmacokinetic/pharmacodynamic (PK/PD) relationship does not exist (20).

The study has some limitations. While we gave MAT2203 for 7 consecutive days by oral gavage, we were only able to dose LAMB for 4 days because the mouse tail after the fourth dose became lacerated from repeated needle injections, making it unsuitable for additional dosing. Furthermore, in the first experiment (Fig. 1A), the higher dose of 45 mg/kg of MAT2203 was not well tolerated by neutropenic mice and we had to drop this dose from subsequent studies.

Despite these limitations, our pre-clinical efficacy studies, coupled with lower toxicity and the additional fact that MAT2203 is administered orally, support continued investigation and development of MAT2203 as a novel, and oral formulation of amphotericin for the treatment of mucormycosis. A major clinical advantage would be to initiate patients with mucormycosis on intravenous LAMB treatment followed by transitioning them to oral MAT2203 treatment.

MATERIALS AND METHODS

Mucorales and culture conditions

R. arrhizus var. *delemar* 99-880 and *M. circinelloides f. jenssenii* DI15-131 are clinical isolates obtained from the Fungus Testing Laboratory at the University of Texas Health Sciences Center at San Antonio (UTHSCSA). These two isolates have been used in our murine mucormycosis models (14, 15). The organisms were grown on potato dextrose agar (PDA) plates for 4–7 days until confluent at 37°C. Spores were collected by flooding the plates with sterile phosphate-buffered saline (PBS) containing 0.01% (vol/vol) Tween 80. The spores were concentrated by centrifugation washed in the PBS, diluted, and counted using a hemocytometer. Targeted inoculum for infection was 2.5×10^5 spores/25 µL for *R. arrhizus* var. *delemar* and 2.5×10^6 spores/25 µL for *M. circinelloides f. jenssenii*.

Susceptibility testing

Mucorales fungi were compared to the activity of LAMB using the (CLSI) M38-A2 method (21).

Immunosuppression

Male CD-1 mice (20–25 g from Envigo, Indianapolis, IN, USA) were used in this study. Immunosuppression was rendered by administration of cyclophosphamide (200 mg/kg, intraperitoneal) and cortisone acetate [500 mg/kg, subcutaneous (s.c.)] on days −2, + 3, and +8 relative to infection. This treatment regimen results ~14 days of leukopenia with total white blood cell count dropping from ~130,000/cm^3 to almost no detectable leukocytes as determined by Unopette System (Becton-Dickinson and Co.) (14). To prevent bacterial infection, 50 mg/L Baytril (enrofloxacin, Bayer, Leverkusen, Germany) was added to drinking water on day −3, then switched to daily ceftazidime (5 mg/mouse, s.c.) treatment starting day 0 through day +13 (22).

Infection and treatment

Immunosuppressed mice were intratracheally infected with 2.5×10^5 spores of *R. arrhizus* var. *delemar* or 2.5×10^6 spores of *M. circinelloides f. jenssenii* in 25 µL using a gel-loading tip after sedation with isoflurane gas (14). Following inoculation, three mice were sacrificed, and their lungs were harvested for quantifying the delivered fungal inoculum by quantitative culturing on PDA plates. Treatment with placebo (diluent control), oral MAT2203 [5–45 mg/kg, given once daily (qd) or twice daily (bid) for 7 days], or intravenous injection of 10 mg/kg qd of LAMB (Gilead Sciences Inc., Foster City, CA, USA) started 16 h post-infection and continued for 7 days for MAT2203 and 4 days for LAMB. Placebo mice received vehicle control. The primary and secondary endpoints were time to moribundity of infected mice (as determined by the criteria of ruffled and/or matted fur, weight loss of >20%, hypothermia, decreased activity, hunched posture, inability to

eat or drink, and torticollis or barrel rolling) and tissue fungal burden in lungs and brains (primary and secondary target organs, respectively) using conidial equivalent by qPCR (23). Histopathological samples were sectioned at 5 µm, and then stained with Grocott methenamine silver stain.

Statistical analysis

For survival studies and from our vast experience with animal models, we expect 10 mice/group would provide at least 80% power to test the hazard ratio of 0.2 or less with a level of significance $P = 0.025$ using the Cox proportional hazard model (one-sided test) assuming 100% and 50% mortality in the test and control group, respectively. For the tissue pathogen burden, 10 mice/group would provide at approximately 90% statistical power to detect the effect size of 2.5 or 2.5 SD difference in CFU (expressed as log) content using a two-sided two sample *t*-test with α of 0.05, assuming the standard deviation of the test group is twice of the one for the control group. For all comparisons, mean ± SD, median (interquartile range), and 95% confidence interval will be computed. All data analyses will be conducted using GraphPad Prism 6. $P < 0.05$ will be considered significant.

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Y.G., T.G., and E.Y. designed, performed, collected, and analyzed the data. S.A. and S.E. performed some of the studies. T.M., J.C., and R.M. conceptualized and aided in the design of the experiments and provided funds to conduct the study. A.S.I. conceptualized and designed the experiments, obtained funding, supervised the project, analyzed the data, and wrote the manuscript. All other authors edited the manuscript.

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Yiyou Gu, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft | Teclegiorgis Gebremariam, Data curation, Formal analysis, Investigation,

Methodology, Writing – original draft | Sondus Alkhazraji, Investigation, Methodology | Eman Youssef, Investigation, Methodology | Sabrina El-Gamal, Investigation, Methodology | Theresa Matkovits, Conceptualization, Funding acquisition, Writing – review and editing | Jenel Cobb, Conceptualization, Funding acquisition, Investigation, Writing – review and editing | Raphael Mannino, Conceptualization, Funding acquisition, Investigation, Writing – review and editing | Ashraf S. Ibrahim, Conceptualization, Data curation, Funding acquisition, Methodology, Writing – original draft

ETHICS APPROVAL

Animal studies were approved by the Institutional Animal Care Use Committee (IACUC) of the Lundquist Institute at Harbor-UCLA Medical Center, according to the NIH guidelines for animal housing and care (approval reference number 22802).

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