Tafenoquine exhibits broad spectrum antifungal activity at clinically relevant concentrations in vitro and decreases lung fungal burden in an invasive pulmonary model of Rhizopus in vivo

G. Dow and B. Smith
60 Degrees Pharmaceuticals LLC, 1025 Connecticut Ave NW, Suite 1000, Washington DC, 20036, USA

Abstract

Background: Tafenoquine is active against a broad range of pathogens and accumulates extensively in the lung. We profiled the susceptibility of fungal pathogens to tafenoquine in vitro and in vivo.

Methods: Minimum inhibitory concentrations [MICs] of medically important fungal pathogens were determined using conventional in vitro assays. The daily maximum tolerated dose [MTD] of tafenoquine was determined in neutropenic mice and the effect of two doses of tafenoquine [MTD and 0.5xMTD] on survival and fungal burden were assessed in Rhizopus and Aspergillus lung infections models.

Results: Mean MICs against panels of yeasts and dimorphic/filamentous fungi were 4.5 and 8.3 ug/mL. The MTD of tafenoquine was 5 mg/kg/day. Against Aspergillus [MIC 16 ug/mL], tafenoquine did not increase survival or decrease fungal burden. Against Rhizopus, [MIC 4 ug/mL], tafenoquine decreased lung fungal burden [by 0.5 logs, P < 0.05 at the MTD] in a dose-related manner. Survival in the high-dose [MTD] tafenoquine group was 30% whereas it was 0% in the vehicle group and in most legacy studies.

Conclusions: Tafenoquine exhibited broad spectrum activity against medically important yeasts and fungi in vitro and a dose-related antifungal effect in a Rhizopus lung infection model at clinically relevant doses.

Keywords: Fungi, lung infections, tafenoquine, yeasts, disease prevention

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Introduction

Fungal infections of the lungs are a major cause of mortality and morbidity in immunosuppressed patients, particularly in transplant recipients [1]. Incidence remains high even when effective antifungal is administered [1]. There is therefore a substantial unmet medical need for additional prophylactic measures.

Tafenoquine was approved by regulators as an antimalarial [2,3] but is active against other pathogens. In particular, it is known to be effective for treatment and prophylaxis of Pneumocystis carinii in immunosuppressed rats [4].

Pre-registration non-clinical studies exhibit that tafenoquine accumulates in lung to a greater degree than any other tissue [see Supplementary Information]. This study evaluated the broader spectrum effect of tafenoquine against fungal spp. in the context of lung infections.

Materials and methods

Investigational agents

Investigational agents were prepared in stock solutions of DMSO at 100 x the concentration (6400 ug/mL) to be tested. Aliquots were stored at -20 °C in polypropylene vials. Drug dilutions were conducted in polystyrene test tubes and MIC assays were performed in U-shaped 96-well polystyrene microtiter trays were used for performing the MIC assays. Tafenoquine was a gift from 60 Degrees Pharmaceuticals LLC.
In vitro susceptibility profiling of tafenoquine against yeasts and fungi

The MICs of tafenoquine were determined against various yeasts, dimorphic and filamentous fungi. Fungi were grown on potato flake or Sabouraud agar, then, on the day of the experiment (0.1 mL) were added to sterile 96-well plates containing 0.1 mL control compounds or tafenoquine in RPMI 1640 (with phenol red and glutamine, but bicarbonate was left out) buffered to a pH of 7.0 ± 0.1 at 25 °C with 0.165 M MOPS (3-[N-morpholino] propanesulfonic acid). Final inocula were 0.4 × 10⁶ to 5 × 10⁶ cells/mL for filamentous fungi and 0.4 × 10³ to 5 × 10² cells/mL for yeasts and dimorphic fungi. The microdilution plates were incubated without agitation at 35 °C. After 24 h incubation for Candida and the Mucorales, 48 h incubation for Aspergillus, the dematiaceous fungi, Fusarium, and Sporothrix, 72 h incubation for Cryptococcus, and Scedosporium, 48–72 h incubation for Coccidioides, Blastomyces, and Emergomyces, and 168 h incubation for Histoplasma, MICs were determined. Two MIC values were determined, one representing the concentration resulting in complete inhibition of growth. One positive comparator/control was representing the concentration resulting in complete inhibition (50% inhibition compared to the growth control), and another representing the concentration resulting in complete inhibition of growth. One positive comparator/control was used for yeast (fluconazole) and three were used for filamentous fungi (fluconazole, posaconazole, and voriconazole), representing current first-line therapies for these fungi. Appropriate quality control and references strains of fungi were included. Negative control wells in each plate contained growth medium without antifungal agents. For each drug including positive controls, each concentration was evaluated once against each isolate.

Immunosuppression protocols and determination of the maximum tolerated dose of tafenoquine in neutropenic mice

Ninety neutropenic ICR mice [28 g on average] were administered vehicle [six mice] or 2.5, 5, 10 or 20 mg/kg/day [21 mice per group] tafenoquine once per day for nine days. Tafenoquine was prepared as suspension in 1% v/v methyl cellulose in 0.2% v/v Tween 80 in sterile water. Immunosuppression was initiated via oral administration of cyclophosphamide in sterile water at a dose of 250 mg/kg and cortisone acetate sub-cutaneously in 0.1% polysorbate 60 at a dose of 250 mg/kg one day prior to administration of the first dose of tafenoquine. Cortisone acetate [250 mg/kg] and cyclophosphamide [200 mg/kg] were administered again via the same method on the fifth day of tafenoquine administration. One day prior to tafenoquine administration, and throughout the remainder of the experiment, drinking water was supplemented with enrofloxacin [50 ppm] to prevent bacterial super-infection. Animals clinically examined/weighed daily and those found moribund were humanely euthanized. For the Aspergillus efficacy studies, the immunosuppression and tafenoquine administration were the same as the above.

The Rhizopus efficacy studies were conducted in a different NIH-contracted laboratory utilizing their standard immunosuppression and bacterial super-infection prevention protocol, which was slightly different from the Aspergillus protocol as follows: Immunosuppression was initiated via administration of 200 mg/kg cyclophosphamide intraperitoneally in sterile irrigation water and 500 mg/kg cortisone acetate (CA) subcutaneously (SQ) in 0.1 mL of 0.05% Tween 80 on the first day of tafenoquine administration. Immunosuppressive drugs were readministered on Days 3 and 8. Enrofloxacin was administered in drinking water from Day 3 to Day 0 [to prevent bacterial super-infection]. This was later switched to ceftazone on Day 0 through Day 13.

Preparation of inoculum and inoculation conditions for the Aspergillus efficacy study

Aspergillus fumigatus clinical isolate 293 (Af293) was utilized and has been described elsewhere [5–7].

Potato dextrose agar (PDA) plates inoculated with the Af293 stock strain conidia were placed in a humidified incubator at 37 °C for 10 days prior to preparation of the conidia suspension for inoculations. On the day of infection, a stock solution of conidial suspension was prepared by irrigating the PDA plates in 0.1% v/v Tween 80 in PBS and scraping with a disposable plastic loop. The conidial suspension was concentrated by high-speed centrifugation and then diluted 1:1000 to 1:10,000 in sterile saline. This was adjusted to yield the required volume and concentration, and viability was confirmed by quantifying colony-forming units after overnight incubation on PDA.

Mice were transferred to an acrylic inhalation chamber in a Class II A2 biosafety cabinet. Conidial suspension [6 mL] was added to the Micro Mist® nebulizer which was then attached to the inhalation chamber and compressed air. Conidia were aerosolized and forced into the inhalation chamber by passing air through the nebulizer at 100 kPa for 15 min. After the first 15 minutes, the remaining conidial suspension [6 mL] was added to the nebulizer and aerosolized over 30 min. Compressed air was discontinued after all the suspension was aerosolized, and animals were exposed to the inoculum for a further 1 h in the inoculum chamber.

Three mice were randomly selected in order to confirm conidial delivery. Animals were sacrificed, and their lungs were removed, weighed, placed in saline, homogenized, and serially diluted [1:10 and 1:100 dilutions]. Dilutions [100 microL of each] were plated on PDA plates in duplicate and incubated at
37 °C for 24 hours. The number of colony-forming units per gram of lung tissue was determined to verify the inoculum.

Preparation of inoculum and inoculation conditions for the Rhizopus efficacy study

*R. delemar* 99-880 was obtained from the Fungus Testing Laboratory, University of Texas Health Science Center, San Antonio and is a standard reference strain for laboratory studies. The organism was grown on PDA plates 37°C for 4–5 days. Sporangiospores were collected in endotoxin free Dulbecco’s PBS containing 0.01% v/v Tween 80, washed, and diluted as appropriate to a final concentration of 1 × 10^7 spores/mL. After sedation with isoflurane gas, and pulling the tongue to the side with forceps, 2.5 × 10^5 spores (in 25 μL of PBS) was injected into the trachea through the vocal cords using a gel-loading tip. Shortly after inoculation, three mice were sacrificed, and their fungal burdens were assessed quantitatively as before to confirm appropriate inoculation.

Efficacy assessments

For the *Aspergillus* study, neutropenic mice received 0 [vehicle, 10 animals], 2.5 or 5 mg/kg/day tafenoquine [10 mice per group] or 20 mg/kg/day posaconazole BID for 10 days [10 mice], used for inoculum verification [n = 3] or left untreated [5 mice]. Immunosuppression and timing of tafenoquine dosing relative to immunosuppression was the same as it was for the MTD study described earlier. Antibacterial prophylaxis was administered via drinking water as described earlier. Mice were inoculated two days after the initiation of immunosuppression as described earlier [this was Day 0]. Clinical signs were assessed twice daily for five days after the last dose of drug administration. The main endpoint was survival through Day 12. Lung fungal burden was assessed by PCR [8] if animals became moribund or at the end of the experiment.

For the *Rhizopus* survival experiment, a neutropenic mice received 0 [vehicle, 10 mice], 2.5 or 5 mg/kg/day tafenoquine [10 mice per group] or liposomal amphotericin B [10 mg/kg IV for four days commencing 24 h post-infusion [10 mice per group], were used for inoculum verification [three mice], or were left untreated [n = 5]. The fungal load experiment had no untreated control group but was otherwise the same. Inoculation was two days after the first dose of immunosuppression [Day 0]. In the survival study, clinical signs were recorded twice daily for 14 days after the last dose of tafenoquine, and the main endpoint was survival at Day 21. In the fungal burden study, lung fungal burden was assessed on Day 4 post-infection by PCR as previously described [9].

Statistical analysis

As fungal burden in the *Rhizopus* study was expected to be lower in the tafenoquine high dose arm than the vehicle, this difference was tested using a one-tailed student’s t-test for unequal variances. As fungal burden in the *Rhizopus* study was expected to be higher in the tafenoquine high dose arm than in the vehicle dose arm, a difference tested using Fisher’s exact test. Differences between other groups in the animal studies were assessed numerically as appropriate.

Ethics approval

Efficacy studies were approved by IACUC committees at the Lundquist Institute and the University of Texas Health Science Center, San Antonio.

Results

Table 1. MICs of tafenoquine and reference compounds against yeasts

| Species/Strain | Tafenoquine MIC [μg/mL] | Fluconazole MIC [μg/mL] |
|----------------|--------------------------|------------------------|
|                | 50% inhibition | Complete suppression |
| Candida parapsilosis | 4 | 1 |
| ATC 22019 | 4 | 22 |
| C. albicans | 8 | 0.5 |
| ATCC 90028 | 4 | 0.25 |
| C. albicans | 4 | > 64 |
| ATCC 90030 | 4 | > 64 |
| C. albicans | 2 | > 64 |
| ATCC 90027 | 4 | > 64 |
| C. glabrata | 8 | > 64 |
| ATCC 90011 | 8 | 8 |
| C. glabrata | 8 | 8 |
| C. guilliermondii | 2 | 2 |
| CG1 | 2 | 2 |
| C. guilliermondii | 4 | 2 |
| CG2 | 4 | 2 |
| C. guilliermondii | 4 | 1 |
| CG3 | 4 | 1 |
| C. neoformans | 4 | 0.5 |
| U50197 | 4 | 4 |
| C. neoformans | 4 | > 64 |
| H99 | 4 | 16 |
| C. neoformans | 4 | 64 |
| CN3 | 8 | NC |
| Average (SD) | 4.5 (1.9) | 4.9 (1.9) |

NC = Not calculated.

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Maximum tolerated dose of tafenoquine in neutropenic mice

Tafenoquine appeared to be well-tolerated in the lower dosage groups [2.5 and 5.0 mg/kg], as the mice in these, and the vehicle control group, appeared healthy and without signs of intolerance. Mice in the higher dose groups [10 and 20 mg/kg] had lost weight relative to mice in vehicle control group by Day 7/8, and two of 21 in the 10 mg/kg tafenoquine group and 4 of 21 in the 20 mg/kg group found moribund prior to the study endpoint and humanely euthanased. Doses of 2.5 and 5 mg/kg were chosen for efficacy evaluations.

Efficacy of tafenoquine against Aspergillus

In the Aspergillus study, survival was enhanced in the posaconazole group but not in the tafenoquine groups [Table 3]. Fungal burdens, as assessed on Day 12 or when mice became moribund, were numerically similar in the high dose and 1 h vehicle groups. In contrast, fungal burden was numerically higher in the vehicle dose group than the 1 h vehicle group. These data are not inconsistent with a fungistatic effect of tafenoquine, although recognized antifungals may increase survival at doses lower than those that are fungistatic [10]. This could not be confirmed by increasing the dose of tafenoquine, as the highest dose used was already the MTD.

Efficacy of tafenoquine against Rhizopus

Since the average ratio of the minimum effective dose [MED] to the fungistatic dose of posaconazole against Aspergillus is < 4 [10], we expected that tafenoquine might provide clinical benefit and exhibit a fungicidal effect against a more susceptible fungal strain. High dose of tafenoquine numerically increased survival and decreased fungal burden against Rhizopus delemar in vivo, with the latter trend reaching the level of statistical significance [Table 4]. Lower dose of tafenoquine exhibited a numerical decrease in fungal burden, implying a dose relationship [Table 4]. The positive control exhibited lower survival than high dose of tafenoquine but a more robust drop in fungal burden [Table 4].
Tafenoquine exhibited a dose-related effect on fungi in this study, as activity in vivo was more pronounced against the more susceptible Rhizopus strain compared to the Aspergillus strain, and the higher dose had a numerically more pronounced effect on fungal burden in both animal studies. Although in this particular experiment the high-dose tafenoquine-induced numerical increase in survival in the Rhizopus study did not reach the level of statistical significance that may be a function of the small sample size [fixed for this primary screening model]. It is known from historical studies in this model that survival in the control group is usually 0%, and never more than 10% [11]. Therefore, the likelihood that the 30% survival rate in the high dose of tafenoquine arm occurred by chance is vanishingly small.

The in vivo efficacy against Rhizopus observed was less pronounced than for other non-malaria species against which tafenoquine has been evaluated. For example, Mordue et al. [12] showed that a single dose of 20 mg/kg cleared Babesia parasites, Yardley et al. [13] showed that tafenoquine exhibited an ED50 of 1.2 to 3.5 mg/kg/day against Leishmania spp, and Queener [4] demonstrated that the minimum efficacious dose against Pneumocystis was 2 mg/kg/day every 4th day for 16 days in rats. Tafenoquine is safe and effective for chemoprophylaxis of malaria in humans [2] and prevents malaria in mice at a dose of 5 mg/kg per day [14]. Tafenoquine increased survival and decreased fungal burden in Rhizopus-infected mice at the same dose and thus is a good pharmacological candidate against fungal lung infections in humans.

It is clear from observing the pattern of susceptibility of fungal isolates to tafenoquine and traditional antimicrobial drugs that there is not cross-susceptibility between them, implying a unique mechanism of action [Tables 1 and 2]. The mechanism of action of tafenoquine against malaria parasites is not definitively known, but vacuolar acidification [like the 4-aminoquinoline chloroquine] or induction of oxidative stress have been suggested [15]. The latter seems more likely, since primaquine, tafenoquine’s progenitor pharmacophore, exhibits selectivity against some malaria parasites stages [but not others] through the action of oxidative intermediates generated in a tissue specific manner, and inhibits the growth of Saccharomyces cerevisiae by cleaving ROS-labile Fe–S groups in key enzymes such as aconitase [16,17]. Also, tafenoquine but not chloroquine, kills babesia parasites in a manner similar to hydrogen peroxide [18]. A systematic evaluation of the mechanism of action of tafenoquine against fungi should now be undertaken.

Tafenoquine is approved for prevention of malaria in adults for up to six months [2], and a recent safety study established a comparable safety profile over a 12-month duration of use [19]. The risk of malaria amongst travelers to West Africa at 54 per 1000 travel years [assuming an average trip length of 1 month] is lower than the risk of pneumonia attributable to fungi of 124 per 1000 person years in transplant patients taking effective antifungal prophylaxis [1,20]. Given the data described herein, and noting also the activity of tafenoquine against another lung pathogen Pneumocystis [4], clinical trials should be undertaken to assess the safety and prophylactic efficacy of tafenoquine for these indications when added to the existing standard of care.

Fungal infections caused by Candida sp. in particular C. auris, are increasing in frequency and becoming more geographically widespread [21]. Many infections caused by C. auris are refractory to azoles, amphothericin B, and echino candins [21]. Tafenoquine exhibits at most a four-fold difference in susceptibility across yeast strains with a 256-fold difference in

**TABLE 3. Fungal burden and survival data for the Aspergillus efficacy study**

| Pharmacologic parameter | Treatment group |
|-------------------------|-----------------|
|                         | 1 h vehicle group | Vehicle | Tafenoquine 2.5 mg/kg | Tafenoquine 5 mg/kg | Posaconazole 20 mg/kg | Uninfected control |
| Mean log10 CFU/g (SD)   | 4.14 (0.29)      | 4.41 (0.34) | 4.36 (0.21) | 4.06 (0.54) | 3.28 (0.32) | 0.0 (0) |
| Survival (%)            | NA              | 0%        | 0%        | 0%        | 80%       | 100%       |

CFU = Colony forming units, NA = Not applicable.

Discussion

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susceptibility to fluconazole, and with a level of potency [MIC \(<8\) ug/ml] that it is expected that the drug could exhibit clinical benefit where there is lung involvement. Further studies are required to assess whether tissue distribution of tafenoquine is consistent with the hypothesis that the drug may be effective alone or in combination with front-line therapies against disseminated yeast infection.

**Conclusion**

Tafenoquine was active against medically important yeasts and filamentous fungi *in vitro* at clinically relevant concentrations. Efficacy studies suggested tafenoquine increased survival and decreased lung fungal burden against a susceptible strain of Rhizopus [MIC 4 ug/ml] in a dose-related manner in a lung infection model at clinically relevant doses. It is expected that tafenoquine at doses approved for malaria prophylaxis in humans will perturb the course of fungal lung infections in humans when utilized alone and/or as an addition to the standard of care.

**Authors’ contributions**

Geoffrey Dow: Conceptualization, Resources, Writing - Original Draft, Writing – Review and editing, Formal analysis, Project administration.; Bryan Smith: Supervision, Writing - Review and editing.

**Transparency declaration**

GSD is the compensated CEO and CSO of 60P, the majority shareholder of 60P, and an inventor on US patents 10342791 and 10888558 and US patent application 17/189544 [and related patents] and has a financial interest in the commercial success of Tafenoquine. BS is an inventor on US patents 10342791 and 10888558 and was paid in his capacity as the Chief Medical Officer of 60 Degrees Pharmaceuticals in relation to participation in this study. These statements are made in the interest of full disclosure and not because the authors believe these statements to constitute a conflict of interest.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nmni.2022.100964.

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