A-1874

Pharmacodynamics of BAL4815, a New Azole Antifungal in a Mouse Model of Systemic Infection

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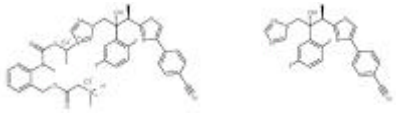
Introduction:

BAL4815 is a new antifungal agent, which belongs to the azoles. BAL4815 is administered as the water-soluble pro-drug BAL8557 (figure 1). In vitro, BAL4815 showed broad-spectrum antifungal activity against *Candida* spp. (including fluconazole-resistant *C. albicans*), *Cryptococcus* spp., *Aspergillus* spp., *Absidia* spp., *Rhizopus* spp., *Rhizomucor* spp., *Histoplasma capsulatum*, and *Blastomyces dermatitidis* [2].



Pro-drug BAL8557 Active drug BAL4815

Figure 1

Aim:

To determine the pharmacokinetic and -dynamic properties of BAL4815 in a non-neutropenic murine model of disseminated *Candida albicans* infection.

Methods:

The MIC of BAL4815 against *C. albicans* UC820 was determined in triplicate using a broth microdilution method [1]. The MIC was the lowest concentration that showed no more than 50% of growth in comparison to the growth control.

The single-dose pharmacokinetics of BAL4815 were determined for individual non-neutropenic, uninfected female CBA/J mice (Janvier, France) following the administration of subcutaneous doses of 10 and 50 mg/kg of the pro-drug BAL8557 in 0.2 ml volumes. For each dose examined, groups of two mice were sampled by retro-orbital puncture up to 24 h after administration of the pro-drug BAL8557.

Methods (continued):

The single-dose pharmacodynamics of BAL4815 were determined in duplicate in non-neutropenic female CBA/J mice. Mice were infected iv with *C. albicans* UC820 2 h prior to the start of therapy. Groups of two mice were treated ip for 72 h with different dosing regimens by using twofold increasing total doses (1.25 to 160 mg/kg/day) administered at 6, 12 and 24 h intervals as the pro-drug BAL8557 in 0.2 ml volumes. Mice were killed after 72 h of therapy, and the kidneys were removed for CFU determination.

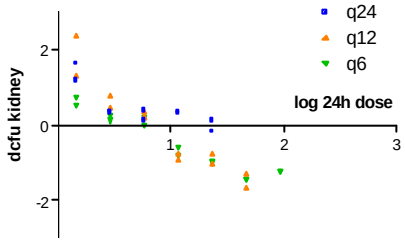


Figure 2.

Relationship between the 24 h total dose and effect (dCFU: difference in CFU at the start of therapy and after three days of therapy) in a non-neutropenic murine model of disseminated candidiasis for three dosing intervals. Symbols above the reference line represent net growth, while those below the reference line represent net killing. Each symbol represents data for one mouse (mean CFU of two kidneys).

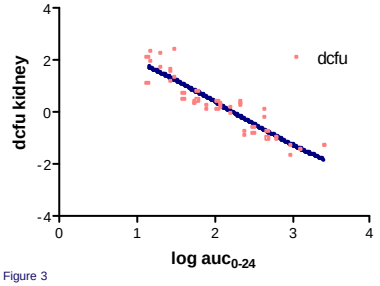


Figure 3

Relationship between fAUC/MIC and dCFU

Results:

The MIC of BAL4815 was 0.004 µg/ml.

The half-life was 3.6 (0.3) h, the volume of distribution was 3.2 (1.0) L/kg and the protein binding was 95.4%.

At the start of therapy kidneys contained 3.62 $\log_{10}$ CFU. After 72 h the kidneys of the untreated control mice contained 7.42 $\log_{10}$ CFU, while the $\log_{10}$ CFU in kidneys of the treated mice varied from 2.16 to 5.60 (q6 h), 2.15 to 5.77 (q12 h) or 3.58 to 5.23 (q24 h). Figure 2 shows the relationship between the 24 h total dose and effect for various dosing regimens. The dose required to produce a net static effect over the 72 h treatment period was independent of the dosing interval. The AUC/MIC correlated best with outcome (r^2=0.81 and 0.86 for the two experiments), with a mean ratio at the EC_{50} and static dose of 222 and 227, respectively for the unbound fraction of the drug.

Conclusions:

- The half-life of BAL4815 in mice was relatively long (3.8 h)
- BAL4815 displayed excellent activity against a disseminated *C. albicans* infection in mice
- The effect was independent of the dosing interval
- AUC/MIC correlated best with outcome

This study was supported by Basilea Pharmaceuticals.

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2. Schmitt-Hoffmann, A., B. Roos, M. Heep, M. Schleimer, E. Weidekamm, et al. Pharmacokinetics of BAL4815, a new azole antifungal, after administration of single ascending intravenous doses of its pro-drug BAL8557. P1033. 14th ECCMID. Prague, Czech Republic.

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