1529. Efficacy of Oral APX001 in a Murine Model of Cryptococcal Meningitis

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Session: 167. Preclinical Study with New Antibiotics and Antifungals
Friday, October 6, 2017: 12:30 PM

Background. APX001 is a first-in-class intravenous and orally available broad spectrum antifungal inhibitor of Gwlt1, a protein involved in glycosylphosphatidylinositol anchor biosynthesis. This study evaluated efficacy of APX001, alone and in combination with fluconazole (FCN), in a mouse model of cryptococcal meningitis.

Methods. Mice (10/group) infected via tail vein with Cryptococcus neoformans received APX001, FCN, both, or neither, for 7 days. APX001 was given orally as 390mg/kg thrice daily. FCN was given intraperitoneally as 80mg/kg/day. Brain and lung were cultured to determine tissue burden. Data were evaluated by unpaired t-test.

Results. In brain, the burden of C. neoformans in mice receiving combined therapy was 3.52 log lower than in untreated control mice. The burden in mice receiving APX001 alone was 0.78 log lower than in untreated mice. The burden in mice receiving FCN alone was 1.04 log lower than in untreated mice. In lung, the burden in mice receiving combined therapy was 1.84 log lower than in untreated control mice. The tissue burden for mice receiving APX001 alone was 1.58 log lower than in untreated mice. The tissue burden in mice receiving FCN alone was 1.3 log lower than untreated mice.

Conclusion. Activity in murine brain: (i) Combined therapy of APX001 with FCN significantly inhibited growth of C. neoformans H99 compared with untreated control mice (P < 0.0001), and was significantly more active than monotherapy with APX001 or FCN (P < 0.0001 and P < 0.0003, respectively). (ii) APX001 and FCN each, alone, significantly inhibited growth of C. neoformans H99 in brain tissue compared with untreated control mice (P < 0.0001). Activity in murine lung: (i) Combined therapy of APX001 with FCN performed somewhat better than FCN alone (P = 0.0397), but no better than APX001 alone (P = 0.2500). (ii) APX001 and FCN each, alone, significantly inhibited growth of C. neoformans H99 in lung tissue compared with untreated control mice (P < 0.0001). (iii) Significant potentiation of APX001 in combination with FCN in this model with C. neoformans H99 was observed within the brain and further investigation is warranted to determine whether APX001 in combination with FCN has potential to be an effective oral regimen for treating cryptococcal meningitis.

Disclosures. K. J. Shaw, Amylex Pharmaceuticals Inc.: Employee, Salary

1530. Diol-Bonded Polymer Microparticles for Treatment of Cutaneous Aspergillosis in an Immunocompromised Murine Model

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Session: 167. Preclinical Study with New Antibiotics and Antifungals
Friday, October 6, 2017: 12:30 PM

Background. Local delivery of antifungals may allow for high concentrations of therapeutic directly in wound beds infected with invasive fungi. In this work, microparticles (MPs) fabricated from a novel biodegradable polymer synthesized from 1,10-decanediol (DD) and fumaric acid were leveraged for the local delivery of voriconazole (VRC) in a murine model of cutaneous aspergillosis. In addition to controlled local delivery of VRC, the MPs also degrade into byproducts which themselves have bioactivity against fungal viability and promote host wound healing.

Methods. The in vitro release kinetics of VRC-loaded MPs were measured over 6 days in PBS at 37°C under mild agitation. Immunocompromised BALB/c mice with 5 mm full thickness cutaneous defects infected with A. fumigatus were treated with: (Group 1) no infection, no treatment; (Group 2) no treatment; (Group 3) unloaded blank MPs; and (Group 4) VRC-loaded MPs (n = 10 per group). Six days after treatment (nine days after initial infection), mice were euthanized. Wound bed, fungal wound bed CFU, and histological presence of fungi were evaluated to determine the effects of MPs on wound healing and infection.

Results. MPs were capable of releasing VRC at concentrations above A. fumigatus MIC at least six days. Mice treated with VRC-loaded MPs had significantly decreased wound size than mice with no treatment (64.2% vs. 19.4% wound reduction, P = 0.002) and were not significantly different than untreated infected controls (64.2% vs. 58.1%, P = 0.497). Although wound healing was increased with VRC-loaded MPs, total fungal burden was not significantly different between infected groups.

Conclusion. Diol-bonded MPs are capable of local delivery of VRC to treat infected wound beds in an immunocompromised murine model of cutaneous aspergillosis. VRC-loaded MPs restored normal wound healing. As fungal burden was unchanged, the exact mechanism of enhanced wound healing needs to be further explored.

Disclosures. D. P. Kontoyiannis, Pfizer: Research Contractor, Research support and Speaker honorarium; Astellas: Research Contractor, Research support and Speaker honorarium; Merck: Honorarium, Speaker honorarium; Cidara: Honorarium, Speaker honorarium; Amplexx: Honorarium, Speaker honorarium; F2G: Honorarium, Speaker honorarium

1531. In vivo Pharmacodynamic Evaluation of Omadacycline (PTK 0796) against Staphylococcus aureus (SA) in the Murine Thigh Infection Model

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Session: 167. Preclinical Study with New Antibiotics and Antifungals
Friday, October 6, 2017: 12:30 PM

Background. Omadacycline is a novel aminomethylcycline antibiotic in development for acute bacterial skin and skin structure infection (ABSSSI) and community acquired bacterial pneumonia (CABP). Omadacycline is a novel targeted antibiotic designed to achieve net stasis and 1-log kill for pathogens with a PK/PD index of 10. The PK/PD index was determined for acute bacterial skin and skin structure infection (ABSSSI) and community acquired bacterial pneumonia (CABP).

Methods. 10 SA strains (4 MSSA, 6 MRSA) were utilized. MICs were determined using CLSI methods. Single dose murine plasma PK was previously determined in our lab and used for PK/PD analyses. The neutrophilic murine thigh infection model was utilized for all treatment studies and drug dosing was by subcutaneous route. Four-fold increasing doses of omadacycline (0.25–64 mg/kg) were administered q12h to groups of mice infected with each strain. Treatment outcome was measured by determining organism burden in the thighs (CFU) at the end of each experiment (24 hours). The Emax Hill equation was used to model the dose–response data to the PK/PD index AUC/MIC. The magnitude of the PK/PD index associated with net stasis and 1-log kill were determined in the thigh model for all strains.

Results. MICs ranged from 0.25–0.5 mg/L. At the start of therapy, mice had 7.1 ± 0.3 log10 CFU/thigh. In control mice, the organism burden increased 2.3 ± 0.3 log10 CFU/thigh over 24 hours. There was a relatively steep dose–response relationship observed with escalating doses of omadacycline. Maximal organism reductions were 4–5 log10 CFU/thigh compared with untreated controls. Stasis and 1-log kill (from start of therapy) was observed by each strain. The AUC/MIC magnitude associated with stasis and 1-log kill endpoints are shown in the table.

Disclosures. Omadacycline demonstrated in vivo potency against a diverse group of SA pathogens including MRSA strains. Stasis 24 hours AUC/MIC targets

| Group (n = 10) | Dose (mg/kg) | AUC/MIC | Stasis | 1 log kill |
|---------------|-------------|---------|--------|-----------|
| Mean          | 13.9        | 23.7    | 45.7   | 78.1      |
| Min           | 13.0        | 21.9    | 31.7   | 70.2      |
| Std Dev       | 4.3         | 10.6    | 31.4   | 79.5      |