Combination Therapy with SCY-078 and Isavuconazole for Treatment of Experimental Invasive Pulmonary Aspergillosis

Vidmantas Petraitis, MD

Assistant Professor of Research in Medicine

Transplant-Oncology Infectious Diseases Program
Weill Cornell Medicine of Cornell University
New York, NY
Invasive Aspergillosis

Major cause of morbidity and mortality in patients with:

- Profound / prolonged neutropenia (< 500 µL / > 10 d)
- Qualitative defects of phagocytic functions
  - Glucocorticosteroid therapy
  - Graft-vs-host disease
  - Acute graft rejection
  - Chronic granulomatous disease
Current Treatment of Invasive Pulmonary Aspergillosis

- Mortality rates of IPA in cancer patients have varied between 13% and 100% depending on the recovery from neutropenia.
- Current treatment of IPA immunosuppressed hosts relies on the administration of antifungal triazoles; however, the overall therapeutic response rate is estimated to be approximately 50-70%.
- Clearly new strategies are needed for more effective treatment of IPA.
Key Targets of Therapy for Aspergillosis

- Echinocandins inhibit (1→3)-β-D-glucan synthesis in the fungal cell wall.

- Triazoles act by inhibition of cytochrome p450 14-α-demethylase, blocking synthesis of cell membrane-stabilizing ergosterol.
SCY-078 is a semisynthetic triterpenoid derivative of the natural product enfumafungin, a potent inhibitor of fungal (1→3)-β-D-glucan synthases. This compound is structurally different from the echinocandins. It represents a new class of antifungal agent suitable for oral and IV administration. Even though it has the same molecular target as the echinocandins, it is structurally distinct and potentially effective against echinocandin-resistant strains.
• Active agent – Isavuconazole

• Inhibits fungal cell membrane biosynthesis through inhibition of ergosterol formation at the level of lanosterol C14-demethylase

• Wide *in vitro* and *in vivo* antifungal activity, including *Candida* spp. and *Aspergillus* spp.
Combination Therapy of IPA

- Based on previous combination studies between echinocandins and antifungal triazoles we hypothesized that this combination may result in a synergistic interaction \textit{in vivo}. 
Combination Therapy of IPA

• We, therefore studied the *in vivo* efficacy of the new extended-spectrum antifungal SCY-078 in combination with isavuconazole in treatment of experimental IPA in persistently neutropenic rabbits.

• The data from this study would provide an experimental rationale and establish a foundation for further clinical evaluation.
Female New Zealand white rabbits weighing 2.8 to 3.6 kg at the time of inoculation were used in this study.

Atraumatic vascular access was established in each rabbit by the surgical placement of a Silastic tunneled central venous catheter.
Materials and Methods

- *Aspergillus fumigatus* - NIH isolate 4215 (ATCC No. MYA-1163)

- Endotracheal inoculation, which was performed on day 2 of the experiments

- Inoculum of $1.25 \times 10^8$ conidia of *A. fumigatus* (250 to 350 µL)

- Induction and maintenance of neutropenia
  - Cytarabine (Ara-C) 525 mg/m² - (days 1-5)
  - Cytarabine (Ara-C) 484 mg/m² - (days 8-9,13-14)
  - Methylprednisolone - 5 mg/kg (days 1 and 2)
Materials and Methods

- **Antibiotics**
  - ceftazidime (75 mg/kg given IV twice daily)
  - gentamicin (5 mg/kg given IV every other day)
  - vancomycin (15 mg/kg given IV daily)
  - were administered daily from day 4 of chemotherapy until study completion for prevention of opportunistic bacterial infections during neutropenia.

- All rabbits received 50 mg/L of vancomycin in drinking water to prevent antibiotic associated diarrhea due to *Clostridium spiriforme*.

- **White blood cell counts**
  - total leukocyte counts were measured by Coulter counter twice weekly.
Untreated Controls (UC)

SCY-078: - 2.5 mg/kg/day IV (SCY2.5)
- 7.5 mg/kg/day IV (SCY7.5)

Isavuconazole (ISA): - 40 mg/kg/day PO (ISA40)

Combination: - SCY2.5+ISA40
- SCY7.5+ISA40

Antifungal therapy was initiated 24 h after inoculation and continued throughout the course of the experiment for 12 days.
Panel of Outcome Variables

- Survival
- Pulmonary lesion scores
- Lung weights
- Residual fungal burden (quantitative cultures)
- Serum galactomannan antigenemia (GMI) detected by the double sandwich enzyme-linked immunosorbent assay (ELISA)
- $(1\rightarrow3)$-$\beta$-D-glucan levels detected by *Limulus* amebocyte lysate assay
Comparisons between the groups were performed by analysis of variance (ANOVA) with Bonferroni’s correction for multiple comparisons or the Mann-Whitney U-test, as appropriate.

Survival was plotted by Kaplan-Meier analysis. Differences in survival of treatment groups and untreated controls were analyzed by log-rank test.
Results
Survival Probability

- $\textbackslash \pmb{\$}$, $p<0.05$, prolonged survival in SCY2.5+ISA40 and SCY7.5+ISA40-treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and ISA40

- £, $p<0.01$, prolonged survival of rabbits treated with SCY2.5+ISA40, SCY7.5+ISA40, ISA40 alone in comparison to that of UC
Pulmonary Infarct Score

- §, p<0.01, decreased infarct scores in SCY2.5+ISA40 and SCY7.5+ISA40 -treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and ISA40
Lung Weight

- *, p<0.05, decreased lung weights in SCY2.5+ISA40 and SCY7.5+ISA40 -treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and untreated controls
Residual Fungal Burden (log CFU/G)

- †, p<0.01, decreased residual fungal burden in SCY2.5+ISA40 and SCY7.5+ISA40, and ISA40-treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and untreated controls.
Expression of Galactomannan Antigenemia

- *p<0.05; lower GMI in rabbits treated with combination regimen of SCY7.5+ISA40 in comparison to that of single therapy of SCY7.5, ISA40, and untreated controls
Expression of Galactomannan Antigenemia

- There was lower GMI in rabbits treated with combination regimen of SCY2.5+ISA40, but did not reach significant differences in comparison to that of single drug therapy
Serum (1→3)-β-D-glucan Levels

- *p<0.05; decrease of serum (1→3)-β-D-glucan levels in SCY7.5+ISA40, SCY7.5, or ISA40-treated rabbits in comparison to that of untreated controls
Serum (1→3)-β-D-glucan Levels

- *p<0.05; decrease of serum (1→3)-β-D-glucan levels in rabbits treated with combination regiment of SCY2.5+ISA40 in comparison to that of single therapy of SCY2.5 and untreated controls
Conclusions

• Rabbits treated with the combination of SCY plus isavuconazole demonstrated
  – prolonged survival,
  – decreased pulmonary injury,
  – reduction of residual fungal burden, and
  – lower serum GMI
  in comparison to those of single therapy of SCY and/or isavuconazole

• These findings provide an experimental rationale and establish a foundation for clinical evaluation of the combination of SCY-078 and isavuconazole for treatment of IPA
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