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Pharmacokinetics of SCY-078 following Intravenous Administration in Rabbits: Implications for Treatment of Experimental Invasive Pulmonary Aspergillosis

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Abstract

Background. Invasive pulmonary aspergillosis (IPA) is a life-threatening infection in immunosuppressed patients that carries high mortality and serious morbidity despite advances in antifungal therapeutics. The emergence of triazole resistance by *Aspergillus fumigatus* adds further urgency to this unmet need. SCY-078 is a semisynthetic derivative of the natural product enfumafungin, a potent inhibitor of fungal β-(1->3)-D-glucan synthases. This compound is structurally different from the echinocandins and has the advantage of having oral bioavailability. Its *in vitro* activity against *Candida* spp. and *Aspergillus* spp. was recently demonstrated. We therefore studied the pharmacokinetics of SCY-078 following intravenous administration in rabbits in order to develop a humanized dosage regimen for treatment of experimental invasive pulmonary aspergillosis.
Methods. Healthy female New Zealand White rabbits weighing 2.6–3.3 kg were used in all experiments. Six rabbits per dosage group received SCY-078 at 7.5, 15, and 30 mg/kg for plasma pharmacokinetics. Blood samples were drawn from each rabbit receiving SCY-078 at the following time points: baseline, 0.5 h, 1 h, 2 h, 4 h, 8 h, 12 h, 18 h, 24 h, and 48 h.
Results. The plasma pharmacokinetic parameters $AUC_{(o-24)}$, Cmax, Cl, and Vd in the dosages administered (7.5 mg/kg to 30 mg/kg) reflected the dose-proportionality of plasma exposure and other parameter profiles that were similar to those of human volunteers studied in phase 1 clinical studies.
Conclusion. Plasma concentrations and exposures of SCY-078 were comparable to those of humans when administered in humanized dosages to NZW rabbits. These findings lay the experimental foundation for further investigation in experiemtnal invasive pulmonary aspergillosis in persistently neutropenic rabbits.

Introduction

Invasive pulmonary aspergillosis (IPA) is a life-threatening infection in immunosuppressed patients, particularly in those with severe and prolonged neutropenia as a consequence of myelotoxic chemotherapy for the treatment of cancer and in those receiving immunosuppressive medication for rejection prophylaxis after organ transplantation or treatment of graft-versus-host disease in allogeneic bone marrow transplantation.

Current treatment of IPA in immunosuppressed hosts relies on the administration of voriconazole. Unfortunately, the overall response rate of invasive aspergillosis to voriconazole remains at approximately 50% to 60% with responses as low as nearly 30% in hematopoietic stem cell transplantation recipient. Moreover, the emergence of triazole-resistant *Aspergillus fumigatus* in the EU and US has further accelerated the need for new antifungal agents. Clearly new antifungal agents and strategies are needed for the treatment of IPA.

SCY-078 is a semisynthetic derivative of the natural product enfumafungin, a potent inhibitor of fungal β-(1→3)-D-glucan synthases. This compound is structurally different from the echinocandins and has the advantage of having oral bioavailability. Its *in vitro* activity against *Candida* spp. and *Aspergillus* spp. has been consistently demonstrated. Laboratory animal studies in predictive models are critically needed to establish the scientific foundation for clinical trials in invasive candidiasis and pulmonary aspergillosis.

We therefore studied the plasma pharmacokinetics of SCY-078 in NZW rabbits across a broad dosage range and analyzed the findings through non-compartmental pharmacokinetics.

Materials and Methods

Animals. Healthy female New Zealand White rabbits (Covance Research Products, Inc., Denver, PA) weighing 2.6 to 3.5 kg at the time of experiments. Vascular access was established by modified surgical placement of a Silastic tunneled central venous catheter as previously described.

All rabbits were monitored under humane care and use standards in facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International, according to the guidelines for the care and use of laboratory animals of the National Research Council and under the approval of the Animal Care and Use Committee of the Weill Cornell Medical Center, New York, NY. Rabbits were individually housed and maintained with water and standard rabbit feed ad libitum.

Materials and Methods

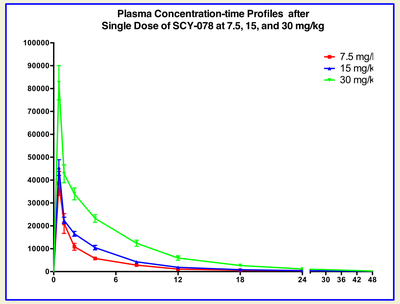
SCY-078 Pharmacokinetics.

Single Dose Pharmacokinetics. Six rabbits per dosage group received SCY-078 at 7.5, 15, and 30 mg/kg for plasma pharmacokinetics. Blood samples were drawn from each rabbit receiving SCY-078 at the following time points: baseline, 0.5 h, 1 h, 2 h, 4 h, 8 h, 12 h, 18 h, 24 h, and 48 h.

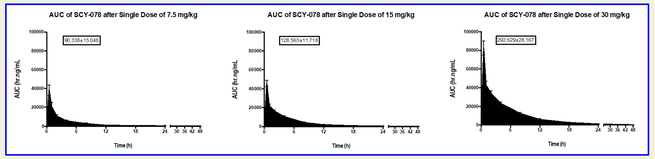
Optimal Sampling Pharmacokinetics in Infected Animals. The plasma pharmacokinetics of SCY-078 were studied in four to six infected animals each per dosage cohort 2.5, 5, 7.5, 10 and 15mg/kg. Time points for sampling were determined by inspection of full plasma concentration profiles obtained in normal rabbits following administration of similar dosages based upon previous plasma pharmacokinetic studies. Plasma sampling was performed on day 7 of antifungal therapy. Blood samples were drawn at baseline and at 0.5 h, 1 h, 2 h, 4 h, 8 h, and 24 h post dosing. Plasma was immediately separated by centrifugation and stored at -80°C until assayed.

Results

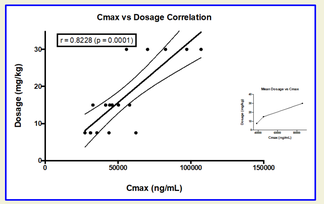
Plasma Pharmacokinetics of SCY-078 after Intravenous Single Dose Administration at 7.5, 15, and 30 mg/kg to Healthy New Zealand White rabbits

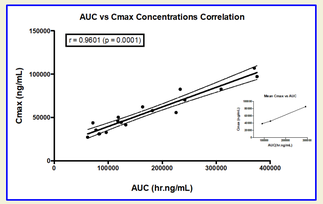


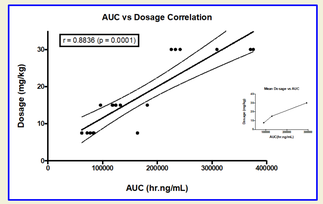
SCY-079 Dose (mg/kg)	$AUC_{(o-24)}$ (hr·ng/mL)	C_{max} (ng/mL)	Cl (L/hr)	Vd (L)
7.5	90,338 ± 15,048	38,533 ± 5,282	0.28 ± 0.03	1.08 ± 0.12
15	128,563± 11,718	45,466 ± 3,443	0.38 ± 0.02	1.66 ± 0.07
30	292,629 ± 28,167	85,583 ± 7,478	0.34 ± 0.04	1.85 ± 0.13



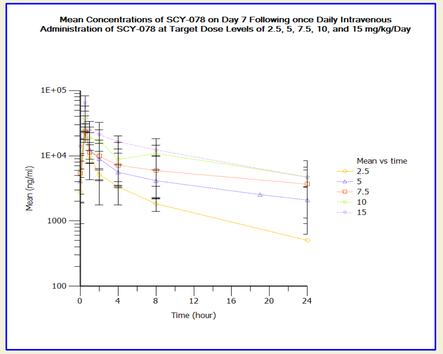
Results

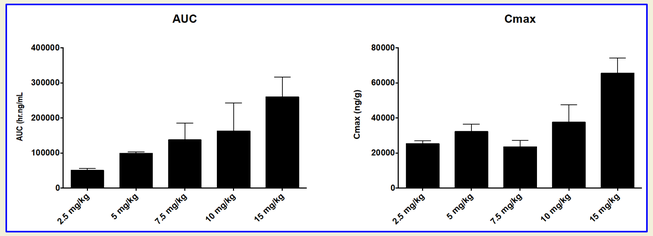


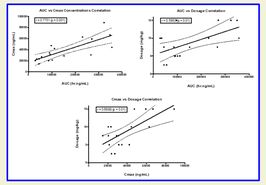


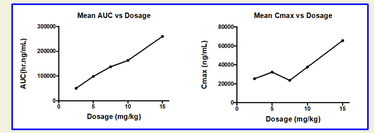


Plasma Pharmacokinetics on Day 7 after Intravenous Administration of SCY-078 at 2.5, 5, 7.5, 10, and 15mg/kg to Healthy New Zealand White rabbits infected with *Aspergillus fumigatus*









SCY-079 Dose (mg/kg)	$AUC_{(o-24)}$ (hr·ng/mL)	C_{max} (ng/mL)	Cl (L/hr)	Vd (L)
2.5	50.384 ± 5,529	25,300 ± 1,700	0.12 ± 0.01	0.78 ± 0.17
5	98,548 ± 4,929	32,250 ± 4,307	0.13 ± 0.02	2.13 ± 0.63
7.5	137,421 ± 48,519	23,550 ± 3,761	0.19 ± 0.05	2.32 ± 0.23
10	162,869 ± 79,897	37,581 ± 9,962	0.35 ± 0.14	1.51 ± 0.28
15	260,041 ± 56,638	65,550 ± 8,689	0.18 ± 0.05	1.64 ± 0.23

Conclusions

- The plasma pharmacokinetic profile of SCY078 demonstrates linear dose proportional pharmacokinetics.
- Clearance remained relatively constant across the dosage range.
- The Vd greatly exceeded the central compartment suggesting distribution into deep tissues.
- These data provide a foundation for further study this novel antifungal agent in treatment experimental candidiasis and aspergillosis.