Polyoxazoline is a suitable biopolymer for the extended release of irinotecan in rats and dogs

Tacey X. Viegas, Michael D. Bentley, Kunsang Yoon, Zhihao Fang, Bekir Dizman, Rebecca Weimer, J. Milton Harris and Randall W. Moreadith

Serina Therapeutics, Inc., Huntsville, AL 35806, USA
tviegas@serinatherapeutics.com

ABSTRACT SUMMARY
Polyoxazoline (POZ) polymers with side chain pendants were prepared and the oncology drug, irinotecan, was attached to each pendant. SER-201 is a POZ polymer with an average of ten irinotecan molecules per polymer backbone. Male and female Sprague-Dawley rats were administered a single intravenous dose of 20 mg/kg of irinotecan or SER-201. Male Beagle dogs were administered intravenous infusions (30 and 60 min) of 15 mg/kg of irinotecan or 15 and 30 mg/kg of SER-201. The plasma concentrations of SER-201, irinotecan and its active metabolite SN-38 were measured by a LC/MS-MS method and the pharmacokinetic (PK) parameters were calculated. Results show that the plasma half-life of irinotecan and SN-38 in rats treated with SER-201 was 159 and 88 h, respectively, when compared to 2 and 5 h, respectively, when treated with irinotecan only. The plasma half-life of irinotecan and SN-38 in dogs treated with SER-201 was 322 and 473 h, respectively, when compared to 38 and 5 h, respectively, when treated with irinotecan only. These results show that POZ is a suitable drug delivery carrier for extended release of irinotecan.

INTRODUCTION
We have developed a class of polymers called polyoxazoline (POZ) with different types of molecular architectures. These patented polymers are of high quality and have side chain pendants for the attachment of small molecular weight drugs, as shown in the cartoon below:

In this presentation we introduce POZ as a drug delivery vehicle that can successfully deliver irinotecan, a topoisomerase I inhibitor, with extended half-lives and drug exposures that are necessary for the treatment of solid tumors. We show that SER-201 has optimal PK parameters when compared to irinotecan.

EXPERIMENTAL METHODS
A 20kDa Polyoxazoline polymer with an average of ten pendant side chains was prepared and purified using Serina’s proprietary technology. Irinotecan was coupled to a small molecule ester linker and then attached to each pendant arm by ‘click chemistry’. The resulting molecule, SER-201, was tested for solubility, purity, and drug loading.

Male and female Sprague-Dawley rats (nine each) were divided in groups of three per sex to allow for a staggered PK blood sampling plan (NMT 5 time points per animal). Each animal received a single intravenous dose of 20 mg/kg of irinotecan or SER-201. Serial blood samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, 96, 120 and 168 h post-dose and plasma processed for bioanalytical analysis.

Six male beagle dogs were used in the study and divided in three groups of two. One group received two infusions of irinotecan at 15 mg/kg, and the other two groups received infusions of SER-201 at doses of 15 and 30 mg/kg. The infusions were of 30 and 60 min durations given three weeks apart. Serial blood samples were collected after each infusion at 0.5, 1, 2, 6, 12 and 24 hours, and subsequently once thereafter on days 3, 4, 6, 8, 11, 15, 18 and 22. The plasma was processed for bioanalytical analysis. Both study protocols were reviewed and approved by in-house institutional animal care and use committees.

The key pharmacokinetic parameters were calculated using the Phoenix WINNONLIN software version 6.2 (Pharsight Corp., Cary NC). The data was fitted to a non-compartmental model.

RESULTS AND DISCUSSION
SER-201 was >99% pure, and soluble in water and 5% dextrose solution. The drug loading was confirmed by Reverse Phase HPLC to be 17% by weight. Gel filtration chromatography and MALDI confirmed the molecular weight of the polymer and H1-NMR confirmed the number of ‘click’ pendants on the molecule.

Figures 1 and 2 are time course plots that show the rat plasma concentrations of irinotecan and SN-38, respectively, following a single intravenous injection of irinotecan and SER-201 at a dose of 20 mg/kg.

Figures 3 and 4 are time course plots that show the dog plasma concentrations of irinotecan and SN-38, respectively following two intravenous infusions of irinotecan and SER-201 three weeks apart, and at a dose of 15 mg/kg.
PK results show that the plasma half-life of irinotecan and SN-38 in rats treated with SER-201 was 159 and 88 h, respectively; in comparison, the half-life was only 1.9 and 4.9 h, respectively, when treated with irinotecan (Table 1).

The plasma half-life of irinotecan and SN-38 in dogs treated with SER-201 was 322 and 473 h, respectively, when compared to 38.5 and 5.4 h, respectively, when treated with irinotecan only (15 mg/kg, 60 min infusion as shown in Table 2).

Intravenous administration of SER-201 significantly reduced the Cmax levels of both irinotecan and SN-38 at both doses, with a marked increase in the volume of distribution. The 60 min infusion in dogs was better tolerated and gave optimal PK parameter values.

CONCLUSION
SER-201 is a viable polymer-drug compound for the extended release of the small molecule drug, irinotecan. POZ is a suitable polymer for the delivery of this compound and other oncolytics.

REFERENCES