Pharmacokinetics of Recombinant Human Annexin A5 (SY-005) in Patients with Severe COVID-19

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AUTHORS

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INTRODUCTION

- Coronavirus disease (COVID-19) pandemic is caused by SARS-CoV-2 virus.[1] Severe COVID-19 is complicated by multiorgan dysfunction, acute respiratory distress syndrome (ARDS), and coagulopathy.[2]
- To date, there have been approximately 7 million COVID-19-related deaths globally (https://covid19.who.int).
- Severe COVID-19 remains a clinical challenge despite available treatment options of tocilizumab and dexamethasone.[3-5]
- Annexin A5 is a ubiquitously expressed protein (~36 kDa). Annexin A5 reversibly binds to negatively charged phospholipids, most notably phosphatidylserine, in a Ca^{2+}-dependent manner. Annexin A5 has anticoagulant, anti-apoptotic and anti-inflammatory properties.[6-8]
- In animal models of sepsis, annexin A5 inhibits pro-inflammatory responses, reduces thrombin generation, and improves organ function and survival.[9-11]
- Since severe COVID-19 is a manifestation of sepsis and involves these same pathways, annexin A5 may be a viable treatment candidate. Recombinant human annexin A5 (SY-005) has been shown to be safe in healthy subjects (NCT04217629) and in severe COVID-19 patients (NCT04748757).[12]
- The pharmacokinetic properties of SY-005 in patients with severe COVID-19 are unknown.

OBJECTIVES

We performed a randomized, double-blind, placebo-controlled pilot trial (NCT04748757) of recombinant human annexin A5 (SY-005) in patients with severe COVID-19.

This study aimed to evaluate the pharmacokinetic properties of SY-005 in patients with severe COVID-19.

METHOD

Study Design
- Randomized, placebo controlled, double blinded trial studying two doses (50 and 100 µg/kg) of annexin A5 (SY-005) administered IV q12h for 7 days in severe COVID-19 patients.

Blood Collection
- Blood was collected and processed within 30 minutes (centrifugation at 1500 *xg* for 15 min).
- Samples were collected prior to SY-005 infusion, directly after infusion (0 min), 15 min, 30 min, 1 hour and 6 hour after infusion.

Annexin A5 ELISA
- Plasma samples were analyzed using a human annexin A5 ELISA kit (AB223863)

Activated Partial Thromboplastin Time (aPTT) and INR of Prothrombin Time
- An aPTT kit (Thermo Fisher) was used to initiate a clot and clotting time was measured using absorbance readings from a microplate reader.
- INR was assessed using Dade Inovin reagent and time of formation of a fibrin clot was measured using a coagulation analyzer (Sysmex CS-2500).

RESULTS

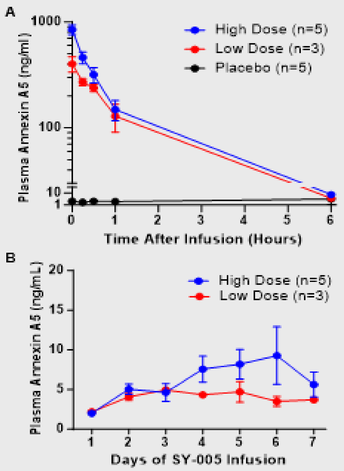

Figure 1. Pharmacokinetics of SY-005 and daily pre-dose plasma annexin A5 levels. (A) Plasma annexin A5 (SY-005) levels return to baseline within 6 hours of SY-005 infusion for both low (50 µg/kg) or high (100 µg/kg) drug doses. **(B)** Pre-drug administration annexin A5 levels throughout the 7 days of the study approach baseline levels without significant accumulation.

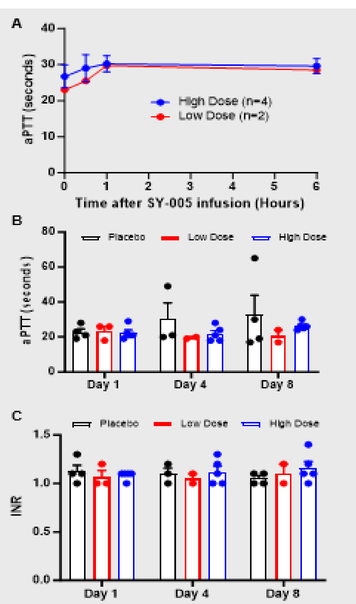

Figure 2. SY-005 does not alter clinical markers of coagulation. (A) Activated partial thromboplastin time (aPTT) during the first 6 hours of SY-005 administration on study day 1. **(B and C)** aPTT and INR measurements, respectively, on study days 1, 4 and 8 before SY-005 or placebo administration. Due to heat inactivation, one sample from each dose group was not suitable for aPTT test resulting in n=4 and n=2 for high and low-dose groups, respectively.

Table 1. Baseline demographics of study patients with severe COVID-19 randomized to placebo, low (50 µg/kg) and high (100 µg/kg) dose SY-005 groups.

Characteristics	Placebo	SY-005 (50 µg/kg)	SY-005 (100 µg/kg)	P value
Number of patients (n)	5	3	5	
Age, years	54 (42-71)	37 (36-52)	46 (42-58)	0.24
Sex, male/female	4/1	1/2	5/0	0.09
Body weight, kg	104.5 (82.0-150.0)	88.0 (76.2-90.0)	93.5 (88.1-137.3)	0.17
Body mass index, kg/m^2	34.1 (30.7-40.6)	29.4 (25.4-38.4)	29.5 (28.3-41.0)	0.54
Serum creatinine, µmol/L	78 (39-96)	46 (44-76)	57 (49-77)	0.36
eGFR, mL/min/1.73m^2	100.2 (84.3-123.7)	122.6 (104.2-122.6)	114.6 (104.4-125)	0.24
Serum albumin, g/L	30 (27-31)	28 (27-34)	30 (25-34)	0.92
Platelet count (x10^9/µL)	270 (215-450)	220 (216-345)	225 (132-431)	0.75
International normalized ratio (INR)	1.1 (1.0-1.3)	1.0 (1.0-1.2)	1.1 (1.0-1.1)	0.71
Endogenous annexin A5 (ng/mL)	2.12 (1.28-12.41)	1.93 (1.75-2.9)	1.99 (1.58-2.61)	0.79

Data are given as median with range in brackets. Chi-square analysis for sex and one-way ANOVA followed by the Kruskal-Wallis test for all other parameters showed no statistical significance among 3 groups. Endogenous annexin A5 plasma levels were determined before SY-005 or placebo treatment.

Table 2. Pharmacokinetics of SY-005 following a 30-min intravenous infusion in severe COVID-19 patients

Parameters	SY-005 (50 µg/kg)	SY-005 (100 µg/kg)	P value
Number of patients (n)	3	5	-
T_{max} (h)	0	0	-
C_{max} (ng/mL)	402.4 ± 116.2	848.9 ± 200.9	0.04
AUC$_t$ (h*ng/mL)	404.8 ± 55.0	551.1 ± 159.4	0.25
AUC$_\infty$ (h*ng/mL)	409.7 ± 54.0	562.0 ± 159.9	0.25
λz (1/h)	0.757 ± 0.024	0.739 ± 0.121	0.79
Half-life, $t_{1/2}$ (h)	0.92 ± 0.03	0.96 ± 0.16	0.79
Clearance (L/h)	7.52 ± 1.56	15.19 ± 7.14	0.07
MRT (h)	0.87 ± 0.06	0.87 ± 0.19	1.00
Vd (L)	9.98 ± 2.33	20.79 ± 8.77	0.07
Vss (L)	6.48 ± 0.89	12.60 ± 4.38	0.07

Data are mean ± standard deviation (SD) and analyzed by Mann Whitney U test. T_{max}, maximum drug time; C_{max}, maximum drug concentration; AUC$_t$, area under the curve until the last observation time; AUC$_\infty$, area under the curve extrapolated to infinity; λz, terminal phase elimination rate constant; MRT, mean residence time; Vd, volume distribution; Vss, steady state volume distribution.

CONCLUSION

- In severe COVID-19, the pharmacokinetics of SY-005 dosed at 50 and 100 µg/kg in patients with normal renal function showed a dose-dependent increase in SY-005 plasma levels, with subsequent rapid clearance within 6 hours of administration.
- SY-005 did not accumulate in plasma.
- There was no significant effect on coagulation during the 7-day study period.
- These data suggest that SY-005 dosed at either 50 or 100 µg/kg achieved blood concentrations in COVID-19 patients with normal renal function without causing harm.
- Further investigation in a larger randomized clinical trial is needed and in preparation.

ACKNOWLEDGEMENTS

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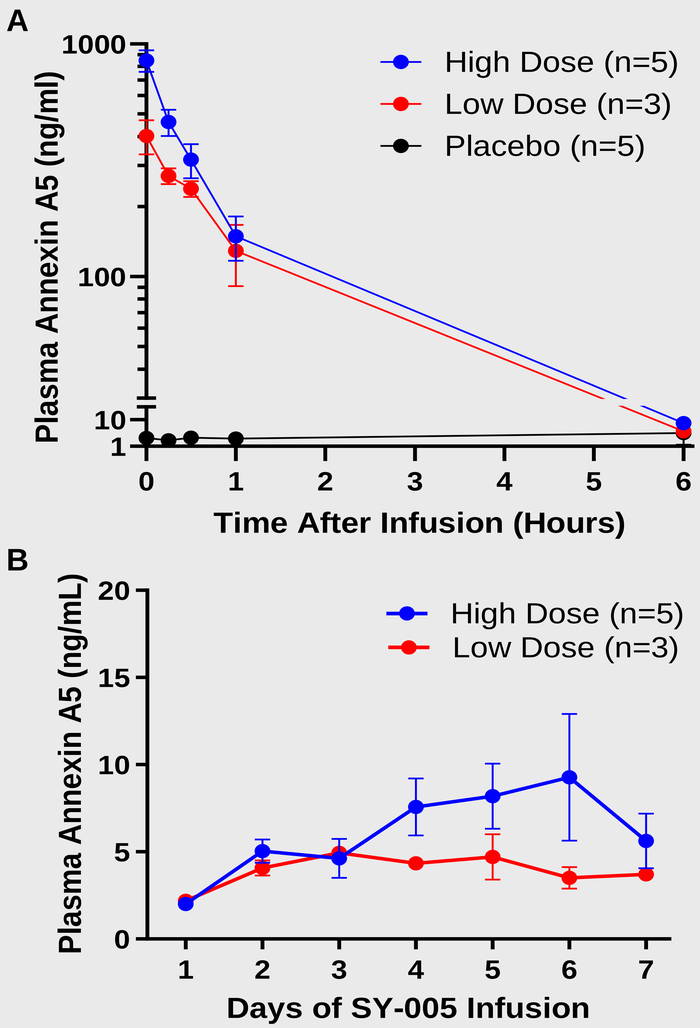

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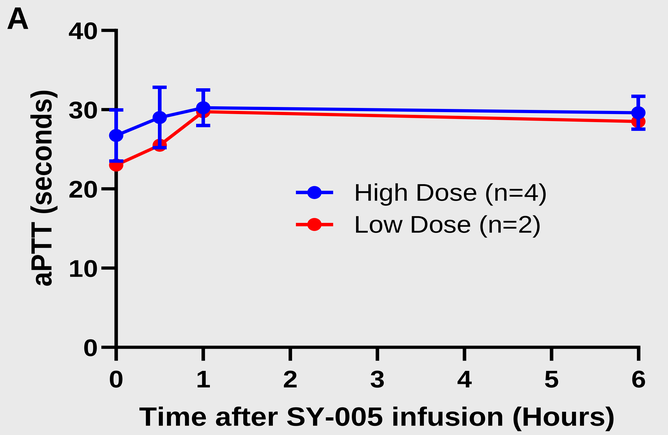

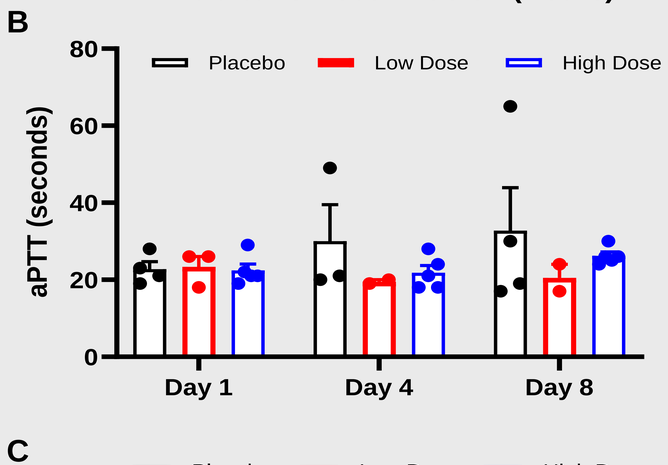

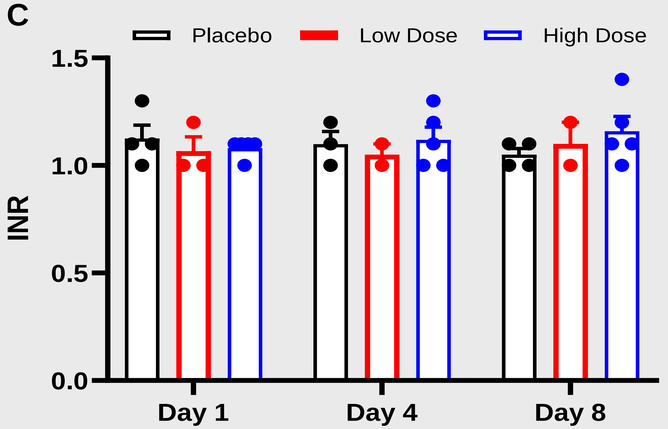

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