A predictive pharmacokinetic model of ribavirin plasma concentration in lung transplant recipients treated for a paramyxovirus or hepatitis E infection.

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Introduction

Ribavirin (RBV) is a guanosine analogue used for treatment of paramyxovirus infections and Hepatitis E in lung transplant recipients (LTR). The pharmacokinetic profile of RBV in the transplant population is unknown and is likely to be altered due to renal and hepatic impairment and cystic fibrosis in these individuals. Two university hospitals (The Netherlands, Australia) use different protocols for RBV consisting of a loading dose followed by oral maintenance dose for 10-14 days. Whilst these protocols have demonstrated efficacy, RBV exposure has not been established. A pharmacokinetic model using observational data and pharmacokinetic modelling was constructed to predict exposure and design an optimal dosing regimen for RBV in this population.

Materials and Methods

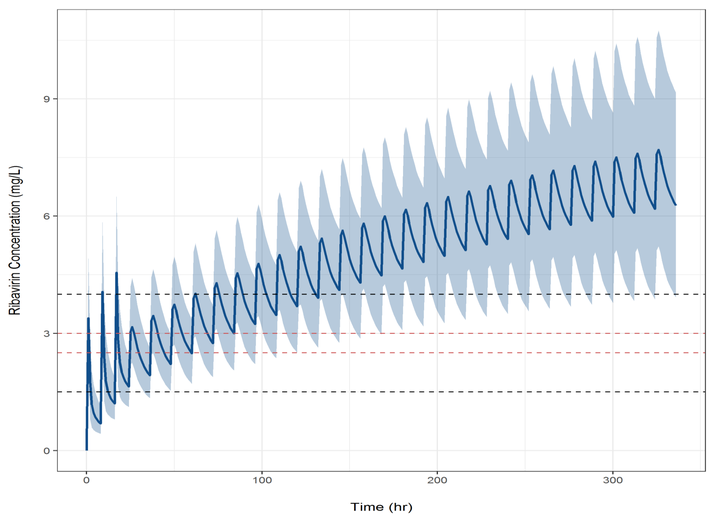
- Two current treatment protocols: mixed regimen (Australia) and purely oral regimen (The Netherlands) were prospectively and retrospectively evaluated.
- Blood samples of LTR were collected per protocol and analyzed using a validated assay.
- Next the concentration-time data was combined with previously published RBV data and used to develop a population pharmacokinetic model using NONMEM® VII software.
- Patient factors contributing to variability were modelled (CrCl, weight, LTR or not, cystic fibrosis or not) and best model was selected.
- The developed model was used to conduct Monte Carlo simulations to evaluate current regimens and predict an optimal dosing regimen.

Results

- Twenty-four LTR with PCR-confirmed PMV or chronic HEV were recruited (13 Dutch protocol/ 11 Australian protocol; 12 male/12 female; Age: 45.3 ± 13.9 yrs; BMI: 23.8 ± 4.82 kg/m^2; CrCL: 69.2 ± 26.7mL/min).
- $Cl_{ribavirin}$ is correlated with CrCl (10% drop in CrCl = 6% drop in $Cl_{ribavirin}$)
- LTR had a 41% reduction in $Cl_{ribavirin}$ compared to healthy controls, no trends for CF, time since Tx or immunosuppressive regimen.
- Current regimens achieved the target concentrations of 1.5-3.0 mg/L within the first 24 hours (figures A and B), but concentrations escalated above toxic levels during maintenance dosing.
- A proposed new regimen prevented this escalation using a lower maintenance dose. (figure C).

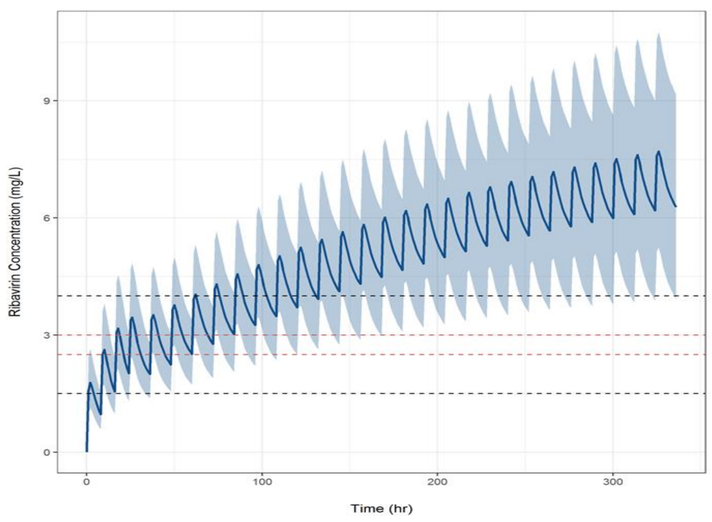
A. Current mixed regimen (Australia)

Day 1: 11mg/kg IV t.i.d. Day 2-14: 10mg/kg Orally b.i.d.



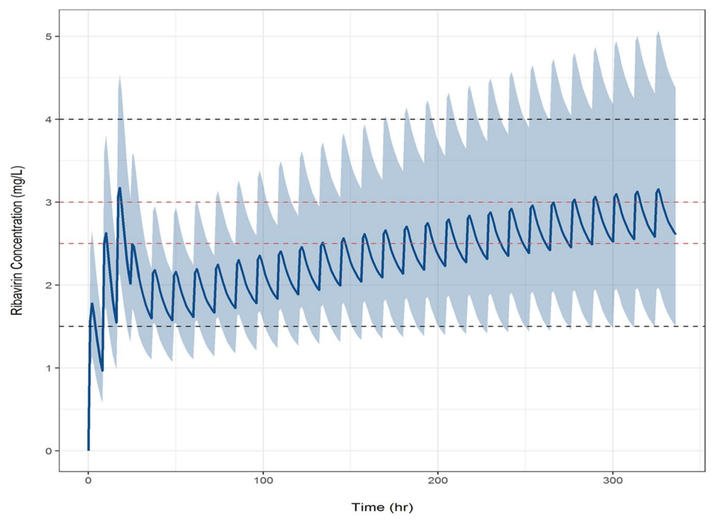
B. Current oral only regimen (Netherlands)

Day 1: 11mg/kg t.i.d. Day 2-14: 10mg/kg b.i.d.



C. Proposed oral only regimen.

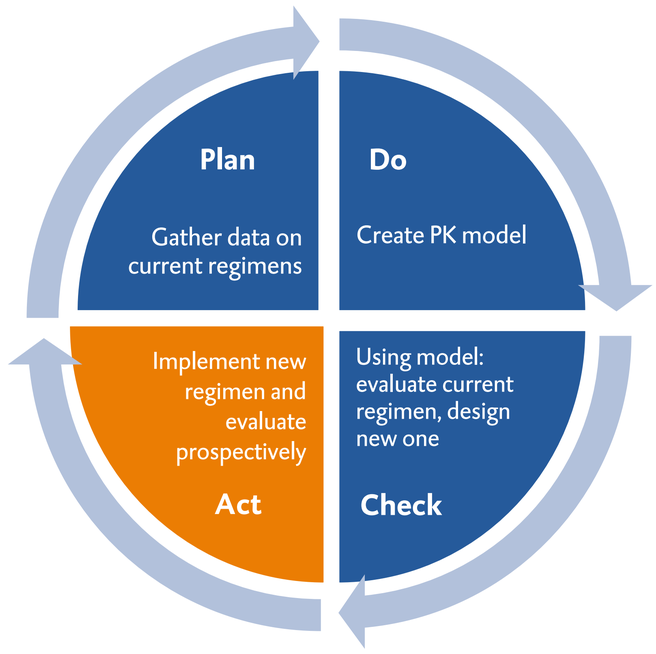
Day 1: 11mg/kg t.i.d. Day 2-14: 4mg/kg b.i.d.



Data presented as median (solid line) and 90% prediction intervals (shaded). Oral doses have been rounded to the nearest 200 mg.

Conclusion

- RBV pharmacokinetics differ in LTR compared to healthy controls mainly due to renal impairment.
- Current protocols reach target concentrations fast, but cause escalation during maintenance treatment.
- A purely oral regimen using 11mg/kg loading dose followed by a 4mg/kg maintenance dose seems practically optimal in quickly reaching an maintaining target concentrations.
- This new regimen will be implemented and evaluated prospectively



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