Title: Repurposed oral ribavirin for respiratory virus infections requires pharmacokinetic-pharmacodynamics for dose optimization.

Authors:

-Auke ES de Zwart (University of Groningen, University Medical Centre Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, the Netherlands)

-Annelies Riezebos-Brilman (University of Utrecht, University Medical Centre Utrecht, Department of Medical Microbiology, Utrecht, the Netherlands)

-Huib AM Kerstjens (University of Groningen, University Medical Centre Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, the Netherlands)

-Erik AM Verschuuren* (University of Groningen, University Medical Centre Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, the Netherlands)

-Jan-Willem C Alffenaar (University of Sydney, faculty of Medicine and Health, School of Pharmacy, Sydney, Australia)

Author contact information:

Auke E.S. de Zwart, corresponding author*

University Medical Centre Groningen, Department of Pulmonary Diseases and Tuberculosis

Secretariaat Longtransplantatie AA33

Hanzeplein 1, PO box 30.001

9700 RB Groningen

email: a.e.s.de.zwart@umcg.nl  T: +31503611778

Keywords: ribavirin, transplantation, pharmacokinetics, RSV, paramyxovirus

© The Author(s) 2019. Published by Oxford University Press for the Infectious Diseases Society of America.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.
Dear Editor,

We have read with great interest the article by Foolad et al. reporting on the use of oral versus inhaled ribavirin (RBV) for the treatment of respiratory syncytial virus (RSV) infection in hematopoietic cell transplant (HCT) recipients in their center. They conclude that oral RBV may be an effective alternative for aerosolized RBV.

While these results are surely promising in light of significant cost savings and availability of treatment, a few questions remain to be elucidated. As the authors stated, neither the optimal dosing regimen nor the optimal treatment duration of RBV are established yet. We recently published the results of a population pharmacokinetic model analyzing current and proposed dosing regimens for RBV in lung transplant recipients. This model examined several dosing strategies using either oral or IV loading doses of RBV followed by oral maintenance dosing. Simulation of a similar regimen as used by Foolad et al. (11mg/kg q8hrs followed by 10mg/kg q12hrs) resulted in quick attainment of target concentrations (2.5-3.0 mg/L), but may result in escalation of concentrations over the course of the treatment period of 14 days, which may cause serious side effects and development of anemia. While Foolad et al. reported treatment for a median of only 5 days, they found no new onset anemia in orally treated patients at day 7, but in 6.9% at day 14. Although there is inter-individual variation in the development of anemia due to variations in several host-factors, hemoglobin may start to fall with plasma concentration >3.5 mg/L. Proposed oral treatment regimens found by our model comprising loading doses of either 11 mg/kg q8hrs for the first 24hrs or 8mg/kg q6hrs for the first 48hrs, followed by a maintenance dose of 4 mg/kg q12hrs or 8 mg/kg q24hrs may quickly attain target concentrations while preventing an overshoot in the RBV concentration and therefore a lower likelihood for developing anemia.

Furthermore as Jain et al stated in their letter, only 18 patients were classified as high-risk leading to a possibly underpowered comparison of the treatment regimens in this important subgroup, while it
is unclear if a benefit of RBV exists in case of mild infections.\textsuperscript{6} We analyzed 96 RSV, parainfluenza and human metapneumovirus infection cases in lung transplant recipients in our center and found that patients with a severe infection, characterized by a $>10\%$ drop in forced expiratory volume in 1 second (FEV1) at presentation, had a worse FEV1 six months post-infection compared to patients with a $<10\%$ drop at presentation. Furthermore, patients with a severe infection who were treated with RBV had a better FEV1 six months post-infection compared to those who received no RBV, while this difference was not present in case of mild infection.\textsuperscript{7}

We emphasize the importance of the study performed by Foolad et al. and support the use of oral RBV in these patients but underline the importance of disease severity regarding treatment decisions/effectiveness and the need for PK/PD research for developing the optimal treatment regimen.

The authors have no conflicts of interest.
References


