Repurposed Oral Ribavirin for Respiratory Virus Infections Requires Pharmacokinetic-pharmacodynamic Dose Optimization

de Zwart, Auke E S; Riezebos-Brilman, Annelies; Kerstjens, Huib A M; Verschuuren, Erik A M; Alffenaar, Jan-Willem C

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Repurposed Oral Ribavirin for Respiratory Virus Infections Requires Pharmacokinetic-pharmacodynamic Dose Optimization

To the Editor—We have read with great interest the article by Foolad et al [1] reporting on the use of oral versus inhaled ribavirin (RBV) to treat respiratory syncytial virus infection in hematopoietic cell transplant recipients in their center. They concluded that oral RBV may be an effective alternative to aerosolized RBV. Although their results are surely promising in light of significant cost savings and availability of treatment, a few questions remain to be answered. As the authors stated, neither the optimal dosing regimen nor the optimal treatment duration of RBV are established yet.

Our group published in 2018 the results of a population pharmacokinetic model analyzing current and proposed dosing regimens for RBV in lung transplant recipients [2]. This model examined several dosing strategies using either oral or intravenous loading doses of RBV, followed by oral maintenance dosing. Simulation of a regimen similar to that used by Foolad et al (11 mg/kg every 8 hours, followed by 10 mg/kg every 12 hours) resulted in quick attainment of target concentrations (2.5–3.0 mg/L) but may result in escalation of concentrations over the 14-day treatment period, possibly causing serious side effects including development of anemia. Although Foolad et al [1] reported treatment for a median of only 5 days, they found new-onset anemia in no orally treated patients at day 7, but in 6.9% of them at day 14. Although there is interindividual variation in the development of anemia, owing to variations in several host factors [3], hemoglobin may start to fall, with RBV plasma concentrations >3.5 mg/L [4, 5]. Proposed oral treatment regimens found by our model, comprising loading doses of either 11 mg/kg every 8 hours for the first 24 hours or 8 mg/kg every 6 hours for the first 48 hours, followed by a maintenance dose of 4 mg/kg every 12 hours or 8 mg/kg every 24 hours, may quickly attain target concentrations while preventing an overly high RBV concentration and therefore reducing the likelihood of anemia.

Furthermore as Jain et al [6] 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, and it is unclear whether RBV is of benefit in mild infections. We analyzed 96 respiratory syncytial virus, parainfluenza, and human metapneumovirus infections 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 (FEV_1) at presentation, had a lower FEV_1 6 months after infection than patients with a <10% drop at presentation. Furthermore, patients with a severe infection who were treated with RBV had a higher FEV_1 6 months after infection than those who received no RBV, but this difference was not present in patients with mild infection [7]. We recognize the importance of the study performed by Foolad et al [1] and support the use of oral RBV in lung transplant recipients, but we also emphasize both the importance of considering disease severity in making treatment decisions and evaluating effectiveness and the need for pharmacokinetic-pharmacodynamic research to develop optimal treatment regimens.

Note

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Auke E. S. de Zwart,[1] Annelies Riezebos-Brilman,[2] Huib A. M. Kerstjens,[1] Erik A. M. Verschuuren,[1] and Jan-Willem C. Alffenaar[3]

[1]Department of Pulmonary Diseases and Tuberculosis, University Medical Centre Groningen, University of Groningen, and [2]Department of Medical Microbiology, University Medical Centre Utrecht, University of Utrecht, The Netherlands; and [3]University Faculty of Medicine and Health, School of Pharmacy, University of Sydney, Australia

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Correspondence: A. E. S. de Zwart, Department of Pulmonary Diseases and Tuberculosis, University Medical Centre Groningen, Secretariaat Longtransplantatie AA33 Hanzeplein 1, PO Box 30.001, 9700 RB Groningen, The Netherlands (a.e.s.de.zwart@umcg.nl).

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Measles, Vaccines, and Types of Perception Bias in Public Debates

To the Editor—Sparked by the resurgence of measles outbreaks, it has become increasingly common in popular media of high-income countries to discuss

advantages and potential risks of vaccines [1–5]. It is a frequently used argument by antivaccine campaigners that, before the 1960s, the decade during which the measles vaccine became available, everybody used to experience these back-then childhood diseases [6], an argument played out to create a connotation of normality and harmlessness concerning an antivaccination choice [1, 3].

However, such an argument contains bias. It is known that bias occurs if comparisons are made between groups that are systematically different with regards to certain characteristics [7]. For example, the act of remembering a specific event may be differential between those who had a disease (or an unfavorable clinical course of the disease) and those without the disease (or a mild course of the disease). Although those with unfavorable clinical courses of measles may be largely in favor of vaccinations, those with mild clinical courses may potentially be opposing it. This is an example of reporting bias [7]. However, as the bulk of measles-attributable population morbidity and mortality in high-income settings occurred before 1970, it is likely that today former patients may not correctly remember the severity of their individual episodes of measles, thus, constituting a form of recall bias [6].

Further, survivorship bias may play a role. It denotes the distorted perception of an exposure (eg, measles episode) when looking only at those with a favorable outcome (eg, survival). Explicit examples are numerous, such as the presumable ease to earn public reputation or fame: for every successful individual (in art, science, politics, etc.), there are, however, potentially hundreds having engaged in the same effort, not having succeeded and thus being lost to the formation of the public perception process [7, 8]. Similarly, in measles vaccination debates, the public opinion is virtually exclusively shaped by those who survived their measles episode in the pre-1970s or had benefitted from vaccination campaigns in the post-1970s. Contrarily, people with a fatal outcome in their measles episode cannot contribute to the public debate anymore to advocate a provaccination choice.

A similar subtype of bias is the so-called visibility bias [9]. It refers to an increased awareness for an exposure (eg, measles) if its outcome is particularly salient or severe (eg, death). Despite a rising measles incidence, the average case-fatality rate of measles is 1:1000 and may still be too low in high-income settings to surpass the public perception threshold [6, 10]. Thus, the absence of public "visibility" of severe clinical outcomes may also be linked to decreased willingness to vaccinate.

Finally, one may even regard the composition of speakers in public debates to be subjected to selection bias. There is broad consensus among medical experts that the measles vaccine is highly efficacious, tolerable, and safe [6, 10]. Thus, a debate hosting the same number of favorers as there are opposers, conveys (whether willingly or unwillingly) a disproportionate medical reality to the audience and an overrepresentation of antivaccine campaigners.

Notes

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Johannes Mischlinger,[1,2] Riko Muranaka,[1,2,3] Silja Bühler,[1,2] and Michael Ramharter[1,2]

[1]Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine and Department of Medicine I., University Medical Center Hamburg-Eppendorf, and [2]German Centre for Infection Research (DZIF), Partner Site Hamburg-Luebeck-Borstel, Hamburg, Germany; and [3]Graduate School of Kyoto University School of Medicine, Japan

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Correspondence: M. Ramharter, Bernhard-Nocht-Str. 74, 20359 Hamburg, Germany (ramharter@bnitm.de).

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Antibiotic Use in Total Knee Arthroplasty Periprosthetic Joint Infection

To the Editor—We have read with much interest the article by Shah et al [1], describing a 29% higher treatment success rate when patients are given an extended course of antibiotics compared with a 6-week treatment course for knee periprosthetic joint infections (PJIs) treated with surgical debridement (debridement, antibiotic therapy, and implant retention [DAIR]).The authors concluded that extended oral antibiotic therapy has