Reply to Fätkenheuer et al

To the Editor—We appreciate the commendation provided by Fätkenheuer et al [1] for our report of the completion of the first randomized therapeutic trial in cancer patients with respiratory syncytial virus (RSV) infections, who were mainly hematopoietic stem cell transplant recipients [2]. However, they raised some concerns regarding the validity of our results, both clinically and statistically, so we appreciate this opportunity to clarify our methods, findings, and conclusions.

As recruitment of patients with RSV infections could be a major hurdle [3], we used a Bayesian adaptive randomization design to allow for comparison of 2 treatment arms without subjecting additional participants to a failing or less beneficial arm during the trial. This approach is often used to overcome the need for large sample sizes and has been used successfully in studies of cancer patients [4].

In response to the comments of Fätkenheuer et al [1] about the clinical plausibility of our results and treatment compliance in both arms of the study, this was an intent-to-treat analysis, and we hypothesized that patients in the intermittent dosing schedule of aerosolized ribavirin (ISR) arm may have better compliance than those in the continuous dosing schedule (CSR) arm, owing to less time spent inside the scavenger tent. Although we used the same dose of 6 g in both arms and saw no differences in tolerability or safety, patients in the CSR arm may not have spent 18 hours in the scavenger test, which is required to receive the full dose of ribavirin. We agree with Fätkenheuer et al [1] that we provided no data to substantiate our hypothesis, but we did not aim this study to measure the differences in compliance rate between the 2 arms.

Fätkenheuer et al [1] also challenged our findings regarding the superiority of ISR over CSR. We refer the readers to Table 1 in our study, which clearly demonstrates an absence of significant differences (except with respect to coinfections) in all baseline characteristics between patients in the 2 treatment arms, which eliminated these risk factors as sources of bias. Only 2 patients who developed RSV pneumonia (the primary outcome for this study) had coinfections, both of which were nonrespiratory [2].

Fätkenheuer et al [1] raised some statistical concerns regarding the randomization procedure. There seems to be some misunderstanding regarding the randomization process. We did not finalize the randomization procedure after enrollment of 10 patients. We randomized the first 10 patients fairly so that each had an equal chance of being assigned to either arm. Starting with the 11th patient, we calculated the randomization probabilities on the basis of the outcomes observed for previous patients, increasing the likelihood of assignment to the treatment arm with better outcomes. We then recalculated the randomization probability for each successive patient on the basis of observed outcomes for previous patients.

Another point raised by Fätkenheuer et al [1] was that the “adaptive randomization process is very sensitive to the characteristics of the first few patients included, and so are all calculations of the accompanying probabilities.” Because of the potential influence of the first few patients, we delayed the adaptive randomization until the 11th patient. Note that 17 (50%) of the first 34 patients were assigned to each treatment arm. For the 35th and subsequent patients, we calculated the probability that ISR has a better response rate than CSR to be >0.90, so by design the randomization probability for ISR was selected as 0.90. Consequently, only 1 of the last 16 patients was assigned to the CSR arm. However, the probability that ISR has a better response rate than CSR never reached the presupposed threshold of 0.95 for terminating the trial early. Our final calculation of the posterior probability that ISR has a better response rate than CSR was slightly less than 0.90 because patient 49, who was assigned to the ISR arm, developed pneumonia after the final patient was enrolled.

Finally, we agree with Fätkenheuer et al [1] that our trial “should not be regarded as proof for the efficacy of aerosolized ribavirin,” as we did not compare either treatment arm with a placebo arm. We based our final argument for recommending ISR on the outcome of this trial and on practical considerations, such as “ease of administration, potentially better compliance, . . ., and acceptance by patients as well as healthcare personnel” [2]. In our conclusion, we reinforced the use of ISR if aerosolized ribavirin is considered and only for cancer patients at risk for progression to pneumonia. We encourage the use of this trial design as a model for future studies of seasonal or uncommon, but serious, acute infections in this vulnerable patient population.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Mark F. Munsell,1 Dimp K. Shah,2 and Roy F. Chemaly2

1Department of Biostatistics and 2Department of Infectious Diseases, Infectious Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas

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Correspondence: Roy F. Chemaly, MD, MPH, Department of Infectious Diseases, Infection Control and Employee Health, Unit 1460, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 (rfchemaly@mdanderson.org).

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