An Adaptive Randomized Trial of an Intermittent Dosing Schedule of Aerosolized Ribavirin in Patients With Cancer and Respiratory Syncytial Virus Infection

Roy F. Chemaly,¹ Harrys A. Torres,¹ Mark F. Munsell,² Dimpy P. Shah,¹ Dhanesh B. Rathod,¹ Gerald P. Bodey,¹ Chitra Hosing,³ Chadi Saifan,¹ Issam I. Raad,¹ and Richard E. Champlin³

¹Department of Infectious Diseases, Infection Control, and Employee Health;

²Department of Biostatistics; and ³Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston

A continuous dosing schedule of aerosolized ribavirin has been used for respiratory syncytial virus (RSV) upper respiratory tract infection and lower respiratory tract infection (LRTI) but is associated with high cost and inconvenient administration. We conducted an adaptive randomized trial to evaluate the effectiveness of an intermittent dosing schedule of ribavirin versus that of a continuous dosing schedule of ribavirin in preventing RSV LRTIs in 50 hematopoietic stem cell transplant recipients or patients with hematologic malignancies. LRTI occurred in 3 patients (9%) receiving the intermittent schedule and in 4 (22%) receiving the continuous schedule, with a 0.889 posterior probability. Because the intermittent schedule is easy to administer and has a higher efficacy than the continuous schedule, we recommend the intermittent schedule for patients who are at risk for RSV LRTI.

Clinical Trials Registration. NCT00500578.

Respiratory syncytial virus (RSV) infection in patients with cancer may progress to lower respiratory tract infection (LRTI), with subsequent high mortality rates [1–3]. In our

recent systematic review on management of RSV infections in adult hematopoietic stem cell transplant (HSCT) recipients, ribavirin use (with and without immunomodulators) was associated with a significant decrease in the incidence of RSV LRTI and mortality [3]. Ribavirin-based therapy initiated at the upper respiratory tract infection (URTI) stage seems to benefit patients with leukemia, as well [4, 5].

Treating every patient is impractical because of the cost, the need for hospitalization and negative-pressure rooms, the discomfort of a continuous dosing schedule of aerosolized ribavirin (CSR), the potential although minimal threat for teratogenicity among healthcare workers, and the lack of randomized clinical trials in which the efficacy of ribavirin has been proven.

CSR has been commonly used, but it can be inconvenient for patients because it increases the difficulty of routine care, as patients must stay in scavenger tents for the duration of therapy, which is usually around 18 hours/day for 5–10 days. However, some patients have been treated effectively with an intermittent dosing schedule of aerosolized ribavirin (ISR) at 2 g administered for 2–3 hours every 8 hours [1].

In the present clinical trial, we used an adaptive randomization study design to compare the safety and efficacy of an ISR and CSR in preventing progression of RSV URTI to LRTI in patients with hematologic malignancies and recipients of HSCT. A secondary aim was to determine the effectiveness of these schedules in decreasing the duration of viral shedding.

MATERIALS AND METHODS

Study Design and Population

This was a prospective, adaptive-randomized, open-label clinical trial involving RSV-infected patients with hematologic malignancy or recipients of HSCT at our institution. The study was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board (ClinicalTrials.gov identifier: NCT00500578).

RSV-infected patients were identified from microbiology laboratory reports from October 2003 through March 2008 and evaluated for study inclusion. Patients were eligible if they had RSV URTI, were >5 years old, and had a hematologic malignancy or underwent HSCT. Patients who were pregnant, were hypersensitive to ribavirin or its components, or had evidence of an RSV LRTI at study entry were excluded. All eligible patients provided written informed consent to participate in the study and were enrolled.

Received 19 March 2012; accepted 4 June 2012; electronically published 22 August 2012.

Presented in part: 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, September 2009.

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).

The Journal of Infectious Diseases 2012;206:1367–71

© The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/infdis/jis516

Enrollment and Follow-up

Patients were randomly assigned to receive CSR (6 g over 18 hours daily) or ISR (2 g over 3 hours every 8 hours daily), administered by a small-particle aerosol generator model 2 with a face mask, for 5–10 days. Follow-up was scheduled for 7–14 days after ribavirin therapy. Patients were evaluated at screening, on day 1 of the study (baseline), on weeks 1 and 2 of the study, at the end of therapy, 7–14 days after completion of therapy, or at study withdrawal. A baseline medical history was obtained, and physical examination along with the following tests were performed within 48 hours after enrollment: complete blood count, beta human chorionic gonadotropin analysis in blood and/or urine specimens (for women of childbearing potential), serum chemistry analysis (to determine blood urea nitrogen, creatinine, bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels), and chest radiography. Nasal wash samples were obtained for RSV culture and antigen detection on days 3, 7, and 14 (± 2 days) and then once weekly for 2 weeks or until 2 consecutive cultures were negative for RSV, whichever occurred first.

End Point Evaluation

The primary end point was progression from RSV URTI to RSV LRTI, with the latter defined as a clinical and radiographic presentation compatible with viral LRTI (ie, onset of respiratory symptoms with new or changing pulmonary infiltrates on chest imaging), with or without abnormal oxygen saturation, in a patient with RSV recovered from bronchoalveolar lavage fluid, sputum, tracheal aspirate, and/or nasal wash samples. The secondary end point was the duration of viral shedding. RSV URTI, neutropenia, and lymphocytopenia were defined according to criteria from a previous study [2]. All patients in this trial received antibacterial therapy, and some received antifungal therapy as part of our standard of care for patients with hematologic malignancy or a history of HSCT who have a respiratory viral infection.

Statistical Analysis

In this schedule selection trial, CSR and ISR arms were compared in terms of treatment failure (ie, progression to LRTI). Initially, patients were randomly assigned equally until 10 patients were assigned to each arm. Then, adaptive randomization was used to unbalance the randomization in favor of the treatment arm having the lower observed failure rate (the operating characteristics of the adaptive-randomization design are shown in [Supplementary Table 1](#)) [6]. The prior distribution of the failure rate for each treatment arm was beta (0.45, 1.05), which had a mean value ($\pm$ SD) of $30\% \pm 29\%$. On the basis of these assumptions and prior clinical experience about the practicality of enrolling such patients in a clinical trial, a sample size of 50 was determined. The Fisher exact test and Wilcoxon rank-sum test were used to assess differences

between the treatment groups with respect to demographic and clinical characteristics. The Kaplan-Meier product-limit estimator was used to estimate the time to clinical response to treatment and duration of viral shedding for both treatment arms at a significance level of 0.05 [7]. The intent-to-treat population included all patients randomized and given at least 1 dose of ribavirin. If the posterior probability for ISR or CSR was >0.95 or if a maximum of 50 patients had received treatment, then the trial would have been terminated, and the superior treatment arm would have been selected.

RESULTS

Study Population, Enrollment, and Adherence

Of the 51 eligible patients, 1 patient was excluded because LRTI was detected prior to therapy. A total of 32 patients were randomly assigned to the ISR arm, and 18 were randomly assigned to the CSR arm (Figure 1).

Both arms had 1 premature discontinuation of ribavirin because of toxicity (ie, chest pain or hepatotoxic effects), with each episode occurring <5 days after therapy initiation. Although neither patient experienced progression to LRTI, for the purpose of our intent-to-treat analysis both were considered to have not responded to treatment. Median durations of ribavirin administration for patients in the ISR and CSR arms were identical (5 days [range, 2–10 days] and 5 days [range, 3–10 days], respectively; $P = .87$).

Patient Characteristics

Most baseline characteristics in the 2 treatment groups were similar (Table 1). Within a month prior to and following the onset of RSV URTI, a significantly higher number of patients in the CSR arm had coinfections (44% vs 16%; $P = .03$). Of the 7 patients who had RSV LRTI, only 2 had coinfections (none had respiratory tract coinfection).

Progression to LRTI

LRTI developed in 3 patients (9%; 90% credible interval, 3.3%–20.0%) in the ISR arm and 4 patients (22%; 90% credible interval, 9%–40%) in the CSR arm. The time to treatment failure, stratified according to the 2 treatment arms, is shown in [Supplementary Figure 1](#). The posterior probability that the rate of progression to LRTI in patients receiving the ISR will be less than that in patients receiving the CSR is 0.889.

Duration of Viral Shedding

The difference in persistence of viral shedding between the 2 treatment groups was not statistically significant (4 days in the ISR arm vs 6 days in the CSR arm [range, 2–28 days for both arms]).

Figure 1. Flow of participants with cancer and respiratory syncytial virus infection through an adaptive randomized trial comparing delivery of aerosolized ribavirin via an intermittent dosing schedule (ISR) and a continuous dosing schedule (CSR).

Toxicity and Adverse Events

We observed no significant differences between the treatment arms with respect to the number of patients with adverse events by maximum grade (grade 4 for the ISR arm and grade 2 for the CSR arm; $P = .99$). Severe adverse events (grades 3–4) are listed in [Supplementary Table 2](#).

Two deaths occurred during the study period (1 per treatment arm), one of which (in the ISR arm) was considered to be RSV related. Bilateral pulmonary infiltrates developed in one of these patients despite use of ISR for 21 days. The patient later had diffuse alveolar hemorrhage that was diagnosed bronchoscopically and deemed to be secondary to RSV LRTI, although bronchoalveolar lavage cultures were negative for RSV. The other patient received CSR. He died of skin, gastrointestinal, and liver graft-versus-host disease 28 days after the end of treatment.

DISCUSSION

To our knowledge, this is the first completed randomized clinical trial of aerosolized ribavirin involving RSV-infected patients with hematologic malignancy and recipients of HSCT. We found that ISR was superior to CSR in preventing

progression from URTI to LRTI. In addition, the resolution of viral shedding, ribavirin tolerability, and safety were similar for the 2 schedules.

Despite a lack of randomized, placebo-controlled trials determining the efficacy of ribavirin for RSV infections in immunocompromised patients, physicians have administered this drug to patients at high risk for these infections in many centers in Europe and the United States over the past 2 decades [3].

Although CSR is the only therapy approved by the US Food and Drug Administration for use in children with RSV infection, ISRs are used in many cancer centers because of their ease of administration. In a randomized pediatric clinical trial, short-term intermittent ribavirin therapy had clinical outcomes similar to those of the standard dosing schedule but better patient access and less environmental release [8]. More recently, in a randomized, controlled, multicenter trial involving RSV-infected HSCT recipients that was prematurely terminated because of slow accrual, use of intermittent ribavirin appeared to be safe. It was also more effective than supportive care at reducing progression to LRTI (11% vs 40%; $P = .51$) and RSV loads [1].

Effective patient recruitment is a common problem in clinical trials studying seasonal respiratory viruses, leading to small

Table 1. Characteristics and Outcomes for Participants With Cancer and Respiratory Syncytial Virus (RSV) Infection Involved in an Adaptive Randomized Trial Comparing Delivery of Aerosolized Ribavirin via an Intermittent Dosing Schedule (ISR) and a Continuous Dosing Schedule (CSR)

Variable	CSR Arm (n = 18)	ISR Arm (n = 32)	P ^a
Characteristic ^b			
Age, y	49 (27–66)	49 (15–73)	.90
Male sex/female sex	9/9	20/12	.55
Race/ethnicity			.99
Black	2 (11)	3 (9)	
Hispanic	3 (17)	5 (16)	
Non-Hispanic white	13 (72)	24 (75)	
HSTC	16 (89)	28 (88)	.99
Allogeneic			.39
Overall	15 (94)	23 (82)	
Related/unrelated	10/5	11/12	
Autologous	1 (6)	5 (18)	
Myeloablative conditioning regimen	5 (31)	15 (54)	.15
Time from HSTC to RSV URTI, d	99 (9–1854)	166 (1–1741)	.72
GVHD ^c			.53
Any grade	12 (70)	16 (57)	
Grade ≥2	5 (42)	12 (75)	.12
Cancer type			ND
Acute lymphocytic leukemia	0	5 (16)	
Acute myelogenous leukemia	4 (22)	7 (22)	
Aplastic anemia	0	1 (3)	
Chronic lymphocytic leukemia	0	5 (16)	
Hodgkin disease	0	1 (3)	
Non-Hodgkin lymphoma	10 (56)	5 (16)	
Myelodysplastic syndrome		1 (3)	
Multiple myeloma	4 (22)	7 (22)	
Cancer status			.99
Cytogenetic relapse	5 (28)	6 (19)	
Partial remission	3 (17)	4 (13)	
Progressive/relapse	0	2 (6)	
Remission	10 (56)	18 (56)	
Stable disease	0	1 (3)	
Unknown	0	1 (3)	
Corticosteroid receipt	10 (56)	14 (44)	.56

Table 1 continued.

Variable	CSR Arm (n = 18)	ISR Arm (n = 32)	P ^a
Neutropenia	2 (11)	3 (9)	.99
Lymphocytopenia	6 (33)	9 (28)	.75
APACHE II score	12 (5–16)	10 (5–16)	.21
ANC, cells/mm ³	2610 (80–11 740)	2670 (90–11 820)	.990
ALC, cells/mm ³	1050 (40–3150)	505 (30–2090)	.560
Coinfection ^{d,e}	8 (44)	5 (16)	.03
Outcome			
Progression to LRTI	4 (22)	3 (9)	.230
Hospitalization, duration, d	8 (5–20)	8 (5–36)	.900
Death	1 (6)	1 (3)	1.00

Data are no. of subjects, no. (%) of subjects, or median value (range).

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; APACHE, Acute Physiology and Chronic Health Evaluation; GVHD, graft-versus-host disease; HSTC, hematopoietic stem cell transplantation; LRTI, lower respiratory tract infection; ND, not done; URTI, upper respiratory tract infection.

^a By the Fisher exact test or the Wilcoxon rank-sum test.

^b At enrollment, unless otherwise indicated.

^c Among recipients of allogeneic HSCTs.

^d Within a month before or after the onset of RSV URTI.

^e Coinfections (few patients had >1) consisted of 2 bloodstream infections (due to *Staphylococcus aureus* and *Acinetobacter lwoffii/junii*), 3 urinary tract infections (due to *Escherichia coli* and *Pseudomonas aeruginosa*), 6 cytomegalovirus infection reactivations, 2 cases of BK virus viremia, 1 case of *Clostridium difficile*-associated diarrhea, 1 case of pulmonary aspergillosis (which occurred 25 days before the occurrence of RSV URTI and had no evidence of new pulmonary infection at enrollment until the end of the study), and 1 case of *Stenotrophomonas (Xanthomonas) maltophilia*-associated pneumonia. The latter patient, a male, received a diagnosis of RSV URTI and initiated ISR after LRTI was ruled out as part of the screening for this trial. Eight days later, he developed a cough and a fever (temperature, 39.1°C), with computed tomography of the chest showing right apical focal ground-glass opacity with bilateral pleural effusions. He underwent testing of multiple nasal wash and bronchoalveolar lavage (BAL) specimens, which were all negative for RSV. His BAL culture was only positive for few *S. maltophilia* and *Candida glabrata* organisms. Therefore, he received a diagnosis of *S. maltophilia*-associated pneumonia and was not considered to have RSV LRTI.

sample sizes with inadequate power to detect meaningful differences between treatment arms. With this in mind, we used adaptive randomization for the present trial. By use of Bayesian statistics, we assigned progressively more patients to the treatment arm with the higher success rate (ie, the ISR arm), thus preventing unnecessary recruitment of patients to the less beneficial treatment arm [9]. The ISR was more effective than the CSR at preventing LRTIs, although their tolerability and safety were similar. Additionally, the ISR was easier to administer than the CSR and more convenient for the patients, as they spent less time in scavenger tents (9 vs 18 hours/day), and for the healthcare workers, thus potentially improving compliance with this regimen, which may explain its high success rate.

The persistence of viral shedding did not differ in the 2 treatment arms. Specifically, the average durations of viral shedding in the ISR and CSR arms were 4 and 6 days, respectively (overall range, 2–28 days). However, the durations were much lower than the average duration of 20 days (range, 7–84 days) among allogeneic HSCT recipients in the study by Avetisyan et al, in which only 10% of patients received ribavirin therapy [10]. We hypothesize that use of aerosolized ribavirin may have greater and more direct impact on viral shedding with important epidemiologic and infection control implications. Apart from the chest pain and hepatotoxic effects we observed in 2 patients, we observed very few moderate-to-severe adverse events in either treatment arm, and those that did occur were not treatment related.

Caution is recommended when interpreting our present data, given the study's open-label design, which may bias assessment of the tolerability and/or toxicity of ribavirin. However, this design is less likely to bias assessment of therapeutic end points. Assessment of radiologic findings along with clinical and microbiologic data on the upper or lower respiratory tract is the standard method of diagnosing LRTIs in patients with RSV infections. Because most of our enrolled patients had RSV URTI after engraftment, our findings may not be applicable to patients with RSV infection occurring in the pre-engraftment period. Another limitation of this trial was the quasi-long period of enrollment of all 50 patients; however, no significant changes occurred in the diagnosis, management, or awareness of RSV infections across the 5 seasons during this study.

In summary, in this first reported randomized trial of treatment of RSV infections with aerosolized ribavirin in patients with hematologic malignancy and recipients of HSCT, we demonstrated that the ISR was more effective than the CSR at preventing progression to LRTI and that the schedules had similar safety profiles and tolerability. Because of the ISR's ease of administration, potentially better compliance than that for the CSR, and acceptance by patients as well as healthcare personnel, physicians should consider using an ISR when administering aerosolized ribavirin for RSV URTIs in patients with cancer who are at risk for progression to LRTIs.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of

data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We thank Donald Norwood for his editorial support.

Financial support. This work was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant CA016672.

Potential conflicts of interest. R. F. C. received grant support from Valeant Pharmaceuticals International for this study and a research grant from ADMA Biologics. All other authors report no potential conflicts.

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.

References

- Boeckh M, Englund J, Li Y, et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. *Clin Infect Dis* **2007**; 44:245–9.
- Chemaly RF, Ghosh S, Bodey GP, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. *Medicine* **2006**; 85:278–87.
- Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. *Blood* **2011**; 117:2755–63.
- Ebbert JO, Limper AH. Respiratory syncytial virus pneumonitis in immunocompromised adults: clinical features and outcome. *Respiration* **2005**; 72:263–9.
- Torres HA, Aguilera EA, Mattiuzzi GN, et al. Characteristics and outcome of respiratory syncytial virus infection in patients with leukemia. *Haematologica* **2007**; 92:1216–23.
- Berry DA, Eick SG. Adaptive assignment vs balanced randomization in clinical trials: a decision analysis. *Stat Med* **1995**; 14:231–46.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* **1958**; 53:457–81.
- Englund JA, Piedra PA, Ahn Y, Gilbert BE, Hiatt P. High-dose, short-duration ribavirin aerosol therapy compared with standard ribavirin therapy in children with suspected respiratory syncytial virus infection. *J Pediatr* **1994**; 125:635–41.
- Giles FJ, Kantarjian HM, Cortes JE, et al. Adaptive randomized study of idarubicin and cytarabine versus troxacitabine and cytarabine versus troxacitabine and idarubicin in untreated patients 50 years or older with adverse karyotype acute myeloid leukemia. *J Clin Oncol* **2003**; 21:1722–7.
- Avetisyan G, Mattsson J, Sparrelid E, Ljungman P. Respiratory syncytial virus infection in recipients of allogeneic stem-cell transplantation: a retrospective study of the incidence, clinical features, and outcome. *Transplantation* **2009**; 88:1222–6.