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Efficacy of Oral Ribavirin in Hematologic Disease Patients with Paramyxovirus Infection: Analytic Strategy Using Propensity Scores

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Few antiviral agents are available for treating paramyxovirus infections, such as those involving respiratory syncytial virus (RSV), parainfluenza virus (PIV), and human metapneumovirus (hMPV). We evaluated the effect of oral ribavirin on clinical outcomes of paramyxovirus infections in patients with hematological diseases. All adult patients with paramyxovirus were retrospectively reviewed over a 2-year period. Patients who received oral ribavirin were compared to those who received supportive care without ribavirin therapy. A propensity-matched case-control study and a logistic regression model with inverse probability of treatment weighting (IPTW) were performed to reduce the effect of selection bias in assignment for oral ribavirin therapy. A total of 145 patients, including 64 (44%) with PIV, 60 (41%) with RSV, and 21 (15%) with hMPV, were analyzed. Of these 145 patients, 114 (78%) received oral ribavirin and the remaining 31 (21%) constituted the nonribavirin group. Thirty-day mortality and underlying respiratory death rates were 31% (35/114) and 12% (14/114), respectively, for the oral ribavirin group versus 19% (6/31) and 16% (5/31), respectively, for the nonribavirin group ($P = 0.21$ and $P = 0.56$). In the case-control study, the 30-day mortality rate in the ribavirin group was 24% (5/21) versus 19% (4/21) in the nonribavirin group ($P = 0.71$). In addition, the logistic regression model with IPTW revealed no significant difference in 30-day mortality (adjusted hazard ratio of 1.3; 95% confidence interval [95% CI] of 0.3 to 5.8) between the two groups. Steroid use (adjusted odds ratio, 5.67; $P = 0.01$) and upper respiratory tract infection (adjusted odds ratio, 0.07; $P = 0.001$) was independently associated with mortality. Our data suggest that oral ribavirin therapy may not improve clinical outcomes in hematologic disease patients infected with paramyxovirus.

Patients with hematologic diseases are likely to be at increased risk of infection with respiratory viruses (1–3), and these virus infections may present variable clinical features ranging from mild upper respiratory tract infection (URTI) to progressed lower respiratory tract infections (LRTI). In immunocompromised hosts, including hematopoietic stem cell transplantation (HSCT) recipients, progression to LRTI is associated with high mortality and morbidity (4), so that antiviral therapy based on the presence of the causative virus is desirable to minimize respiratory virus-related mortality (5). Oral neuraminidase inhibitors have been widely used in severe influenza infections, but limited antiviral agents are available against noninfluenza respiratory viruses such as members of the *Paramyxoviridae* family, including respiratory syncytial virus (RSV), parainfluenza virus (PIV), and human metapneumovirus (hMPV).

Inhaled ribavirin has been demonstrated to reduce severe viral infections in noninfluenza respiratory viral infections (6), but widespread use of aerosolized ribavirin has been impeded by its high cost, teratogenicity to health care workers, and potential for side effects such as sudden deterioration of respiratory function (5). To avoid such aerosol ribavirin-related problems in patients with hematologic diseases, treatment with oral rivabirin has been suggested in paramyxovirus infections (3, 7). Small, noncomparative studies reported improvement in the outcomes of respiratory virus infections with oral ribavirin therapy (8, 9). However, limited comparative data are available on its impact on clinical outcomes in patients with paramyxovirus infections (10, 11). We therefore evaluated the effect of oral ribavirin on clinical outcomes in paramyxovirus infections in patients with hematological diseases.

MATERIALS AND METHODS

Study setting. We reviewed the records of the microbiology laboratory admitted to the Asan Medical Center, a 2,700-bed tertiary-care hospital in Seoul, South Korea, from January 2009 to February 2012, to identify patients who were infected with respiratory viruses. In cases of suspected respiratory infections, respiratory virus PCR tests were routinely performed in our center. Patients who were PCR positive for respiratory viruses were identified from the computerized database of the clinical microbiology unit. The study was approved by our hospital ethical committee.

Definitions. All adult inpatients with hematologic diseases who were infected by RSV, PIV, or hMPV with/without other pathogens were included in the study. Patients with influenza, adenovirus, and rhinovirus but without RSV, PIV, and hMPV coinfection were excluded. If a patient had recurrent episodes of respiratory virus infection during the study period, only the first episode was considered. Upper respiratory infection was defined as detection of viruses in upper respiratory secretions, along with symptoms involving the nose and throat (4). Lower respiratory infection was defined as the presence of either hypoxia or pulmonary infiltrates, along with identification of viruses in upper or lower respiratory secretions (4, 7). The pneumonia severity index (PSI) (12) and Curb-65 (13) were evaluated to predict the prognosis of patients, as described elsewhere (14, 15). Coinfection was defined as bacterial, other viral, or fungal infection within 3 days prior to or after the first positive respiratory virus

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PCR. Underlying respiratory death was defined as death due to either pneumonia or viral respiratory infection (16, 17).

The decision to give antiviral treatment was at the discretion of each attending hematologist after receiving an infectious diseases consultant staff member's opinion (S. H. Kim). The oral ribavirin therapy group was defined as patients who received oral ribavirin therapy, and the nonribavirin therapy group was defined as patients who received supportive care with/without steroid or immunoglobulin but without ribavirin. In the ribavirin therapy group, oral ribavirin was given at a dose of 15 to 20 mg/kg of body weight per day in three divided doses (4), and treatment was continued until patients were asymptomatic or virus was not detected.

Virological evaluation. Respiratory viral infection was diagnosed by detecting antigen in microbiological examinations: nasopharyngeal aspirates, swab specimens for URTI, or BAL fluid specimens were obtained, and multiplex reverse-transcription PCR (RT-PCR) was performed for RSV, hMPV, PIV, influenza virus, adenovirus, enterovirus, rhinovirus, human coronavirus, and bocavirus, by Seeplex RV15 ACE detection (Seegene Inc., Seoul, Republic of Korea). The respiratory virus multiplex RT-PCR kit used in this study was evaluated in a previous study (18). Shell vial culture was used for virus isolation (Diagnostic Hybrids, Inc., Athens, OH).

Statistical analysis. A propensity score for each patient—the probability of receiving treatment—was estimated by fitting a multiple logistic regression model, including gender, age, diagnosis, type of virus, HSCT, underlying disease, McCabe score, Charlson comorbidity score, PSI, Curb-65, initial absolute neutrophil count, creatinine, initial hemoglobin, use of immunosuppressive agent, use of steroid, site of infection, and immunosuppression. Model discrimination was assessed with c-statistics ($c = 0.846$) and model calibration with Hosmer-Lemeshow statistics ($x^2 = 1.4324$, $df = 8$, $P = 0.994$) (19, 20). For the propensity-matched case-control study, patients who received oral ribavirin treatment were matched with patients in the untreated group by the Greedy matching algorithm (a 1:1 match) (20–23). This algorithm matches each patient receiving ribavirin treatment with one not receiving ribavirin treatment, with the individuals of each pair having propensity scores that are identical for the first 5 digits (23). If this cannot be done, the algorithm then proceeds sequentially to the next highest digit match to make "second-best" matches, in a hierarchical sequence which continues to a 1-digit match on propensity score for those who remained unmatched (19, 23). After all of the propensity score matches were made, we assessed the balance in baseline covariates between the two intervention groups with the paired *t* test or the Wilcoxon signed-rank test for continuous variables and the McNemar's test or the marginal homogeneity test for categorical variables. In addition, a logistic regression model with inverse probability of treatment weighting (IPTW) using propensity scores was performed to reduce the effect of selection bias in assignment for oral ribavirin therapy (24, 25). All tests of significance were two tailed, and a *P* value of ≤0.05 was considered significant. All statistical analyses were performed with SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Study population. During the study period, 737 patients were tested for respiratory virus infection in our hospital. Among them, 145 patients in the hematologic center were diagnosed with PIV (64 [44%]), RSV (60 [41%]), and hMPV (21 [15%]) infection. Of these 145 patients, 114 (78%) received oral ribavirin therapy, and the remaining 31 (21%) received nonribavirin therapy. The baseline clinical characteristics of the two groups are shown in Table 1. Baseline clinical characteristics were similar between the two groups. However, there were more cases of severe underlying disease (rapidly fatal in the McCabe classification) in the nonribavirin group (52%) than in the ribavirin group (30%, $P = 0.02$), and fewer of the patients in the nonribavirin group received intravenous immunoglobulin (IVIG) during their infections than did those treated with oral ribavirin (10% versus 27%, $P = 0.04$).

Clinical outcomes with and without oral ribavirin treatment. Clinical outcomes in the two groups are shown in Table 2. Treatment with oral ribavirin took place for a median duration of 12 days (interquartile range [IQR], 7 to 16), and the oral ribavirin was used at a median dose of 900 mg (IQR, 900 to 1,200) daily. Follow-up RT-PCR examination was carried out on 75 patients (66%) in the ribavirin therapy group and 4 patients (13%) in the nonribavirin therapy group ($P < 0.001$). The proportions of negative results for viral RNA detection at follow-up were similar in the two groups (60% [45/75] versus 50% [2/4]), although the number of follow-up cases in the nonribavirin group was small. Viral clearance occurred at a median of 16 (IQR, 9 to 22) days after ribavirin treatment. Seven (6%) patients developed adverse symptoms during ribavirin therapy; four developed hemolytic anemia, 2 developed nephrotoxicity, and 1 developed a drug rash. Ribavirin therapy was discontinued in these patients with adverse events.

The ribavirin treatment group required longer hospital stays (median, 20 days) than the control group (median, 10 days, $P = 0.002$). However, 30-day mortality was not significantly different in the two groups ($P = 0.21$). In addition, there was no significant difference in underlying respiratory deaths: 12% (14 of 114 patients in the ribavirin group; 5 with RSV, 5 with PIV, and 4 with hMPV) versus 16% (5 of 31 patients in the control group; 3 with RSV and 2 with PIV) ($P = 0.56$).

Propensity score-matched case-control study. We performed a propensity score-matched case-control study to reduce the effect of potential confounding factors and selection bias. Forty-two patients in 21 pairs were successfully matched for propensity. Twenty-one case patients who received ribavirin treatment were matched with 21 patients derived from the 31 potential control patients. We were unable to adequately match propensity scores for the 10 (32%) other control patients. These 10 unmatched control subjects had the following characteristics: propensity score (mean ± standard deviation [SD]), 0.82 ± 0.24; age (years; mean ± SD), 45.5 ± 16.0; and a 30-day mortality rate of 33% (2 of 6). Baseline clinical characteristic of the matched patients are shown in Table 1. These additional analyses showed that there were no significant differences in covariate balance between the two groups, including McCabe and Jackson scores, coinfection, and use of received immunoglobulin (IVIG) (Table 1). Treatment with oral ribavirin was applied for a median duration of 11 days (IQR, 9 to 16) in the 21 matched pairs, and viral clearance occurred at a median of 11.5 (IQR, 9.0 to 18.5) days after ribavirin treatment. The median length of hospital stay after viral infection was also similar in the two groups after the propensity score-matched analysis (13 days versus 11 days) (Table 2). Thirty-day mortality rates were not significantly different in the two groups ($P = 0.71$). There were 3 cases of underlying respiratory deaths in the ribavirin group (1 RSV and 2 PIV) and 4 in the control group (2 RSV and 2 PIV).

Risk factors for 30-day mortality and a logistic regression model with covariable adjustment and IPTW using propensity scores. A multivariate logistic regression model was analyzed to identify factors affecting mortality (Table 3). Adjuvant steroid use and lower respiratory infection were independently associated with mortality (adjusted odds ratio [OR], 5.67, and 95% confidence interval [95% CI], 1.97 to 16.33; and adjusted OR, 0.08, and 95% CI, 0.02 to 0.35, respectively). However, treatment with oral

TABLE 1 Baseline clinical characteristics

Characteristic	Value[a]				
	Unadjusted model			Propensity score-matched analysis	
	Oral ribavirin therapy ($n = 114$)	Nonribavirin therapy ($n = 31$)	*P* value	Oral ribavirin therapy ($n = 21$)	Nonribavirin therapy ($n = 21$)	*P* value
Age, median yrs (IQR)	47 (35–58)	53 (40–61)	0.09	55 (45–68)	50 (39–60)	0.23
Male gender	67 (59)	14 (45)	0.18	11 (53)	10 (47)	>0.99
Site of infection			0.75			0.51
Upper respiratory infection	37 (32)	11 (35)		5 (24)	8 (38)	
Lower respiratory infection	77 (68)	20 (65)		16 (76)	13 (62)	
Diagnosis			0.12			>0.99
Acute myeloid leukemia	53 (46)	7 (22)		8 (38)	6 (28)	
Acute lymphoblastic leukemia	23 (20)	8 (26)		3 (14)	5 (24)	
Chronic myeloid leukemia	3 (3)	1 (3)		1 (5)	0	
Non-Hodgkin lymphoma	12 (11)	3 (10)		2 (10)	2 (10)	
Other	23 (20)	12 (39)		7 (33)	8 (38)	
Type of virus			0.24			0.80
Respiratory syncytial virus	48 (42)	12 (39)		10 (47)	7 (33)	
Human metapneumovirus	19 (17)	2 (6)		2 (10)	2 (10)	
Parainfluenza virus	47 (41)	17 (55)		9 (43)	12 (57)	
HSCT	58 (51)	16 (52)	0.94	9 (43)	10 (47)	>0.99
Type of transplant						
Allogeneic, sibling	37/58 (64)	10/16 (63)		6/9 (67)	6/10 (60)	NA
Allogeneic, family donor other than sibling	6/58 (10)	2/16 (12)		2/9 (22)	1/10 (10)	
Allogeneic, unrelated	15/58 (26)	4/16 (25)		1/9 (11)	3/10 (30)	
Stem cell source			0.20			
Bone marrow	19/58 (33)	8/16 (50)		4/9 (44)	5/10 (50)	NA
Peripheral blood	39/58 (67)	8/16 (50)		5/9 (55)	5/10 (50)	
Underlying disease state			0.07			0.92
Remission	14 (12)	9 (29)		5 (24)	4 (19)	
Minimal residual	19 (17)	3 (10)		2 (10)	2 (10)	
Persistent/relapse	73 (64)	15 (48)		10 (47)	12 (57)	
Unclear	8 (7)	4 (13)		4 (19)	3 (14)	
McCabe score			0.02			>0.99
Nonfatal	0	0		0	0	
Ultimately fatal	80 (70)	15 (48)		12 (57)	11 (53)	
Rapidly fatal	34 (30)	16 (52)		9 (43)	10 (47)	
Charlson comorbidity score, median (IQR)	2 (2–2)	2 (2–3)	0.71	2 (2–3)	2 (2–2)	0.96
Curb-65			0.97			>0.99
Score 0–1	96 (84)	27 (87)		10 (47)	11 (53)	
Score 2–5	18 (16)	4 (13)		11 (53)	10 (47)	
Pneumonia severity index			0.31			>0.99
I	5 (4)	4 (14)		0	3 (14)	
II	16 (14)	2 (6)		3 (14)	1 (5)	
III	35 (31)	10 (32)		8 (38)	8 (38)	
IV	45 (40)	10 (32)		5 (24)	7 (33)	
V	13 (11)	5 (16)		5 (24)	2 (10)	
Coinfection	44 (39)	9 (29)	0.33	9/21 (43)	5/21 (24)	0.39
Bacterial	19/44 (43)[b]	6/9 (67)[c]		5/9 (55)	2/5 (40)	
Viral	13/44 (30)[d]	2/9 (22)[e]		3/9 (33)	2/5 (40)	
Fungal	12/44 (27)[f]	1/9 (11)[g]		1/9 (11)	1/5 (20)	

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TABLE 1 (Continued)

Characteristic	Value[a]					
	Unadjusted model			Propensity score-matched analysis		
	Oral ribavirin therapy ($n = 114$)	Nonribavirin therapy ($n = 31$)	*P* value	Oral ribavirin therapy ($n = 21$)	Nonribavirin therapy ($n = 21$)	*P* value
Immunosuppressive agent use	43 (38)	8 (26)	0.22	6 (28)	5 (24)	>0.99
Methylprednisolone use	81 (71)	20 (65)	0.48	16 (76)	15 (71)	>0.99
Initial ANC (/mm^3), median (IQR)	1,412 (84–3,980)	1,610 (384–4,947)	0.39	1,984 (336–6,950)	1,270 (180–2,670)	0.47
Initial creatinine, median (IQR)	0.7 (0.6–1.0)	0.7 (0.6–1.5)	0.23	0.8 (0.7–1.0)	0.6 (0.6–0.9)	0.57
Initial bilirubin	0.9 (0.6–1.5)	0.8 (0.7–1.5)	0.93	1.2 (0.8–1.9)	0.8 (0.7–1.8)	0.27
Use of intravenous immunoglobulin	31 (27)	3 (10)	0.04	3 (14)	2 (10)	>0.99

[a] Data are presented as numbers (%) of patients unless otherwise specified. IQR, interquartile range; HSCT, hematopoietic stem cell transplantation; NA, not applicable; ANC, absolute neutrophil count.
[b] Includes *Staphylococcus aureus* ($n = 4$), *Acinetobacter baumannii* ($n = 3$), *Enterococcus faecium* ($n = 2$), *Stenotrophomonas maltophilia* ($n = 2$), *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Staphylococcus epidermidis*, *Chryseobacterium meningosepticum*, *Legionella pneumophila*, *Escherichia coli*, and *Enterococcus faecalis*.
[c] Includes *S. aureus* ($n = 2$), *E. faecium* ($n = 2$), *L. pneumophila*, and *E. coli*.
[d] Includes cytomegalovirus ($n = 4$), parainfluenzavirus ($n = 3$), coronavirus ($n = 2$), rhinovirus ($n = 2$), adenovirus, and enterovirus.
[e] Includes influenza A virus and RSV.
[f] Includes aspergillosis ($n = 8$; 4 possible IPA, 4 probable IPA), *Pneumocystis jirovecii* ($n = 2$), *Candida glabrata* ($n = 2$).
[g] Includes mucormycosis.

ribavirin did not significantly affect 30-day mortality ($P = 0.43$). Careful adjustment was made, using covariable adjustment with the propensity scores, and IPTW using the propensity scores, to reduce the effect of potential confounding factors and selection bias. These additional analyses confirmed that there were no significant differences in lengths of hospital stays after virus infection or 30-day mortality between the two groups (Table 4).

Subgroup analysis of patients infected with respiratory syncytial virus. Because the reported rate of progression to lower respiratory tract disease is higher with RSV than with other respiratory viruses (2), we performed a subgroup analysis in patients with RSV (Table 5). Of these 60 patients, 48 (80%) received oral ribavirin therapy. In general, baseline characteristics were similar in the two groups. Five coinfecting viruses were isolated in the

TABLE 2 Comparison of outcomes

Outcome	Value[a]					
	Unadjusted model			Propensity score-matched analysis		
	Oral ribavirin therapy ($n = 114$)	Non-ribavirin therapy ($n = 31$)	*P* value	Oral ribavirin treatment ($n = 21$)	Non-ribavirin therapy ($n = 21$)	*P* value
Adverse effects of treatment			NA			NA
Hemolytic anemia	4	NA		1	NA	
Nephrotoxicity	2	NA		0	NA	
Drug rash	1	NA		0	NA	
Length of hospital stay after viral infection, median days (IQR)	20 (11–39)	10 (4–23)	0.002	13 (10–25)	11 (4–25)	0.49
7-day mortality	6 (5)	4 (13)	0.14	1 (5)	4 (19)	0.34
14-day mortality	11 (10)	5 (16)	0.34	1 (5)	4 (19)	0.34
30-day mortality	35 (31)	6 (19)	0.21	5 (24)	4 (19)	0.71
Underlying respiratory death	14 (12)	5 (16)	0.56	3 (14)	4 (19)	>0.99
Subgroup analysis for 30-day mortality[b]						
Upper respiratory infection	5/37 (14)	1/11 (9)	>0.99	0	0	NA
Lower respiratory infection	30/77 (39)	5/20 (25)	0.27	5/16 (31)	4/13 (30)	>0.99[c]
Pneumonia severity index						
Risk classes I–III	12/56 (21)	3/16 (19)	>0.99	0	2/12 (17)	0.48[c]
Risk classes IV–V	23/58 (39)	3/15 (20)	0.29	5/10 (50)	2/9 (22)	0.35[c]
With coinfection	21/44 (48)	4/9 (44)	>0.99	4/9 (44)	3/5 (60)	>0.99[c]
Without coinfection	14/70 (20)	2/22 (9)	0.34	1/12 (8)	1/16 (6)	>0.99[c]
HSCT recipient	20/58 (34)	5/16 (31)	0.81	1/9 (11)	3/10 (30)	0.58[c]

[a] Data are presented as numbers (%) of patients unless otherwise specified.
[b] Subgroup analysis was conducted for 30-day mortality of each group.
[c] Fisher exact test or Pearson χ^2 test.

TABLE 3 Logistic regression analysis of risk factors for 30-day mortality[a]

Variable	Multivariate analysis	
	OR (95% CI)	*P*
Use of oral ribavirin	1.55 (0.52–4.56)	0.43
Use of steroid	5.67 (1.97–16.33)	0.01
Upper respiratory infection	0.08 (0.02–0.35)	0.001
PSI risk classes I–III	0.64 (0.28–1.48)	0.30

[a] OR, odds ratio; PSI, pneumonia severity index.

TABLE 4 Comparison of outcomes by multiple logistic regression analysis and inverse probability of treatment weighting[a]

Outcome	Model	Adjusted HR (95% CI)	*P* value
Length of hospital stay after viral infection	Unadjusted model	2.15 (1.36–3.41)	0.001
	PS-matched analysis	1.32 (0.68–2.56)	0.42
	IPTW	1.50 (0.94–2.40)	0.09
Overall mortality	Unadjusted model	1.85 (0.70–4.90)	0.22
	PS-matched analysis	1.33 (0.31–5.79)	0.71
	IPTW	1.94 (0.65–5.78)	0.24

[a] HR, hazard ratio (oral ribavirin therapy was compared with no therapy [reference]); CI, confidence interval; PS, propensity score; IPTW, inverse probability of treatment weighting method.

patients treated with oral ribavirin (2 coronavirus, 1 adenovirus, 1 rhinovirus, and 1 cytomegalovirus), and only one patient, who was infected with coronavirus, died due to progression of viral infection. One patient in the nonribavirin therapy group was coinfected with influenza A virus. This patient developed pneumonia, which was considered incidental to his death.

The median length of hospital stay was longer in the case group (24 days) than in the control group (5 days, $P = 0.002$). About one-third of the patients in both groups died (27% versus 33%), and there were no significant differences in 30-day mortality or in deaths related to the RSV infection ($P = 0.73$ and $P = 0.19$, respectively). A multivariate logistic regression model was also analyzed to identify factors affecting mortality in patients with RSV (Table 6). Upper respiratory tract infection was independently associated with mortality (adjusted OR, 0.07; 95% CI, 0.01 to 0.65). However, treatment with oral ribavirin did not significantly affect 30-day mortality ($P = 0.28$).

DISCUSSION

Although some of the prevalent paramyxoviruses, such as PIV, RSV, and hMPV, can cause significant morbidity and mortality in patients with hematologic diseases and in solid organ transplant recipients, data regarding the usefulness of antiviral therapy in adult patients are limited (1, 26–29). Ribavirin is one of the few available treatment modalities for adult patients with these viral infections. However, there is a paucity of available data describing the effect of ribavirin in adults (26), especially the oral form. In the present study, we found that administration of oral ribavirin for RSV, PIV, or hMPV infections did not reduce mortality in adult patients with hematologic malignancies.

Aerosol ribavirin therapy with or without IVIG or palivizumab has been frequently used in severe noninfluenza respiratory virus infections, although the efficacy of these treatments has not been established (8, 30). However, aerosol ribavirin is not only costly but also causes many aerosol-related side effects, including bronchospasms and teratogenic effects on health care workers (5, 31). In addition, careful administration of aerosol ribavirin through a ventilator is needed to prevent crystallization in the ventilator circuit (1). The alternative of intravenous ribavirin has been proposed for severe RSV infection (29). However, the intravenous form is not approved in the United States (5) or in South Korea. The use of oral ribavirin for respiratory viral infections has been reported in a few studies (3, 7–9). A pilot study conducted by Chakrabarti et al. showed that 5 episodes with RSV infection and 2 episodes with PIV infection in 7 HSCT recipients improved with oral ribavirin therapy (3). Khanna et al. reported that 90% of 25 patients receiving oral ribavirin exhibited a decrease in RSV load of 2 $\log_{10}$ copies/ml within 7 to 14 days (7). Recently, Pelaez et al. reported that 5 lung transplant recipients with RSV pneumonia had favorable outcomes after oral ribavirin therapy (30).

However, without comparing oral ribavirin therapy with some comparator, it is impossible to draw any conclusions about whether oral ribavirin therapy alters the natural course of RSV infection in immunocompromised patients. To our knowledge, no comparative studies on patients with hematologic diseases have been performed except for two recent studies (10, 11). One of these, on lung transplant recipients infected with paramyxovirus, reported that 30-day graft function recovery was higher in the oral ribavirin group (84%, 32/38) than in the nonribavirin group (59%, 17/29) (10). The other study, comparing 6 lung transplant recipients who received oral ribavirin with 15 patients who received inhaled ribavirin, showed that there were no significant differences in 6-month outcomes between the two groups (11). However, ribavirin treatment assignment itself could bias the outcome in this type of observational study. Therefore, we compared outcomes in the oral ribavirin therapy group with those of a comparator group with hematologic diseases, using a powerful statistical tool to compensate for the bias created by treatment assignment in observational studies. One, a propensity-matched case-control study, revealed that baseline clinical characteristics were as similar as in a randomized trial (Table 1). The other, using logistic regression models with covariable adjustment and IPTW using propensity scores, also showed that oral ribavirin therapy did not significantly affect outcomes (Table 4). We think that the agreement between these different analytic approaches strengthens our findings on this important clinical question.

We therefore believe that oral ribavirin is not associated with better outcomes compared with no antiviral therapy. One possible explanation for this result could be variable oral bioavailability of oral ribavirin (32). The absence of any recommended optimal dose of oral ribavirin may have contributed to the conflict between our results and those reported in previous studies, although the median dose was similar in all the studies (4, 7–9). Therefore, we recommend that oral ribavirin should be used with great caution in patients with hematologic malignancies and noninfluenza respiratory virus infections until the results of further experimental animal studies or prospective clinical trials are available.

Some immunomodulators are used in the treatment of paramyxovirus infections. Corticosteroid has been frequently used in severe paramyxovirus infection (11, 33) as well as in severe influenza virus infection (34). However, recent studies on severe pandemic H1N1 influenza (23, 35) and severe RSV (36) demon-

TABLE 5 Baseline clinical characteristics and outcomes in patients infected with RSV[a]

Characteristic	Oral ribavirin therapy ($n = 48$)	Nonribavirin therapy ($n = 12$)	*P* value
Age, median years (IQR)	50 (32–59)	48 (41–60)	0.50
Male gender	27 (56)	6 (50)	0.70
Site of infection			0.17
Upper respiratory infection	13 (27)	6 (50)	
Lower respiratory infection	35 (73)	6 (50)	
Diagnosis			0.36
Acute myeloid leukemia	25 (52)	3 (25)	
Acute lymphoblastic leukemia	10 (21)	3 (25)	
Chronic myeloid leukemia	1 (2)	0	
Non-Hodgkin lymphoma	4 (8)	2 (17)	
Other	8 (17)	4 (33)	
HSCT	26 (54)	8 (67)	0.43
Type of transplant			>0.99
Allogeneic, sibling	14/48 (54)	4/12 (50)	
Allogeneic, family donor other than sibling	2/48 (8)	1/12 (12)	
Allogeneic, unrelated	10/48 (38)	3/12 (38)	
Stem cell source			0.23
Bone marrow	11/48 (42)	5/12 (63)	
Peripheral blood	15/48 (58)	3/12 (37)	
Underlying disease state			0.13
Remission	5 (10)	4 (33)	
Minimal residual	8 (17)	3 (25)	
Persistent/relapse	33 (69)	5 (42)	
Unclear	2 (4)	0	
McCabe score			0.16
Nonfatal	0	0	
Ultimately fatal	36 (75)	6 (50)	
Rapidly fatal	12 (25)	6 (50)	
Charlson comorbidity score, median (IQR)	2 (2–2)	2 (2–2)	0.48
Curb-65			0.91
Score 0–1	39 (81)	10 (83)	
Score 2–5	9 (19)	2 (17)	
Pneumonia severity index			0.62
I	2 (4)	2 (17)	
II	8 (17)	0	
III	16 (33)	4 (33)	
IV	17 (36)	3 (25)	
V	5 (10)	3 (25)	
Immunosuppressive agent use	15 (31)	2 (17)	0.48
Methylprednisolone use	32 (67)	8 (67)	>0.99
Initial ANC (/mm^3), median (IQR)	1,262 (57–4,445)	1,367 (681–4,125)	0.62
Initial creatinine, median (IQR)	0.7 (0.5–0.9)	1.1 (0.6–2.1)	0.05
Initial bilirubin	0.7 (0.6–1.3)	0.8 (0.6–1.6)	0.39
Use of intravenous immunoglobulin	15 (31)	1 (8)	0.15
Follow-up viral test	38 (79)	2 (17)	<0.001
Negative result for viral RNA detection	24/38 (63)	0	0.15
Length of hospital stay after viral infection, median days (IQR)	24.0 (13.5–47.5)	5.0 (2.5–10.0)	0.002
Coinfection	16 (33)	4 (33)	>0.99
Bacterial	9/16 (56)	3/4 (75)	
Viral	5/16 (31)	1/4 (25)	
Fungal	2/16 (13)	0	
Overall mortality	13 (27)	4 (33)	0.73
Underlying respiratory death	5 (10)	3 (25)	0.19

[a] Data are presented as numbers (%) of patients unless otherwise specified.

TABLE 6 Logistic regression analysis of risk factors for 30-day mortality in patients infected with RSV[a]

Variable	Multivariate analysis	
	OR (95% CI)	*P*
Use of oral ribavirin	0.39 (0.07–2.14)	0.28
Use of steroid	3.29 (0.75–14.55)	0.12
Upper respiratory infection	0.07 (0.01–0.65)	0.02
PSI risk classes I–III	0.71 (0.20–2.50)	0.59

[a] OR, odds ratio; PSI, pneumonia severity index.

strated that corticosteroid may adversely affect outcomes (23, 35) and reveal no clinical benefit (36). Thus, our finding that steroid use was associated with 30-day mortality (Table 3) is consistent with other studies (23, 35). Previous studies (1, 37) have shown that ribavirin used in conjunction with IVIG may be more effective in reducing viral load than ribavirin alone. In the present study, even though more patients in the oral ribavirin group (27%) received IVIG than among the untreated patients (10%), there was no significant difference in mortality between the two groups. The net clinical outcomes of such adjuvant treatments are the result of interplay between viral clearance and the immune response. More favorable outcomes might be achieved by controlling viral load with an antiviral agent while reducing the tissue damage caused by the immunomodulating agent used. However, we assume that oral ribavirin therapy is not strong enough to control viral load in patients with RSV infection. Therefore, there is a need for further studies to identify better antiviral agents and/or combination regimens that improve outcomes in patients with severe respiratory virus infections.

This study had a few limitations. First, it was performed in a single center, thus limiting the generality of our results. Second, due to the retrospective and observational nature of the study, only measured covariates were controlled, and there may be additional confounding factors not accounted for. However, considering the seasonality of respiratory virus infections and the slow accrual of patients, it is not easy to conduct randomized controlled trials (1). Hence, it seems valid to perform studies like ours with adjustment for potential differences. Third, this study was performed in patients with hematologic diseases who were infected with paramyxovirus. Thus, caution is called for in extrapolating to other immunocompromised hosts, including solid organ recipients (11, 30). Further studies of this issue are needed.

In conclusion, our data suggest that oral ribavirin therapy may not improve clinical outcomes in hematologic disease patients infected with RSV, PIV, or hMPV. Although oral ribavirin is cost-effective and less of a health hazard than the aerosolized form, it may not be the optimal treatment for infections caused by respiratory virus.

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