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RESEARCH

Outcome of Human Parainfluenza Virus infection in allogeneic stem cell transplantation recipients: possible impact of ribavirin therapy

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Abstract

Background This retrospective study focused on analyzing community-acquired respiratory virus (CARV) infections, in particular human parainfluenza virus (hPIV) after allogeneic stem cell transplant (allo-SCT) in adults recipients. It aimed to assess the impact of ribavirin treatment, clinical characteristics, and risk factors associated with lower respiratory tract disease (LRTD) progression and all-cause mortality.

Patients and methods The study included 230 allo-SCT recipients diagnosed with hPIV between December 2013 and June 2023. Risk factors for the development of LRTD, disease severity, and mortality were analyzed. Ribavirin treatment was administered at physician discretion in 61 out of 230 cases (27%).

Results Risk factors for LRTD progression in multivariate analysis were corticosteroids > 30 mg/day (Odds ratio (OR) 3.5, 95% Confidence Interval (C.I.) 1.3–9.4, $p = 0.013$), fever at the time of hPIV detection (OR 3.89, 95% C.I. 1.84–8.2, $p < 0.001$), and absolute lymphocyte count (ALC) $< 0.2 \times 10^9$/L (OR 4.1, 95% C.I. 1.42–11.9, $p = 0.009$). In addition, the study found that ribavirin therapy significantly reduced progression to LRTD [OR 0.19, 95% C.I. 0.05–0.75, $p = 0.018$]. Co-infections (OR 5.7, 95% C.I. 1.4–23.5, $p = 0.015$) and ALC $< 0.2 \times 10^9$/L (OR 17.7, 95% C.I. 3.6–87.1, $p < 0.001$) were independently associated with higher day + 100 after hPIV detection all-cause mortality. There were no significant differences in all-cause mortality and infectious mortality at day + 100 between the treated and untreated groups.

Conclusion ALC, corticosteroids, and fever increased the risk for progression to LRTD while ribavirin decreased the risk. However, mortality was associated with ALC and co-infections. This study supports further research of ribavirin therapy for hPIV in the allo-HSCT setting.

Keywords Human parainfluenza virus · Respiratory viral infection · Ribavirin · Allogeneic hematopoietic stem cell transplantation · Immunodeficiency scoring index · Community acquire respiratory virus

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Introduction

Human parainfluenza viruses (hPIV), including hPIV-1, hPIV-2, hPIV-3, and hPIV-4, belongto the P*aramyxoviridae*, a group of enveloped, single-stranded negative-sense RNA viruses. They are responsible for causing upper and/or lower respiratory tract diseases (URTD/LRTD) in humans. Among these community-acquired respiratory viruses (CARVs), hPIV-3 is the most frequently identified subtype (> 80%) [1] and is linked to a heightened risk of LRTD and increased mortality in allogeneic hematopoietic stem cell transplant (allo-SCT) recipients [2–4]. The incidence of hPIV infection in allo-SCT recipients varies widely (from 3 to 27%) [5, 6]. LRTD is reported in a range of 7–50% of cases [7–9], and mortality rates associated with hPIV-induced LRTD can be as high as 27% [9]. Among the risk factors for progression to LRTD and increased mortality, the most identified conditions include, lymphocytopenia [10, 11], corticosteroids use at the time of infection [3, 10, 12] and co-infections [13].

Treatment options for hPIV infections are presently constrained, with antiviral therapy employing ribavirin being a potential approach. However, the efficacy of ribavirin in preventing or managing the development of LRTD and reducing mortality remains a subject of contention. Most retrospective studies have not shown a statistically significant benefit of ribavirin on these outcomes although ribavirin was usually used in severe and desperate cases [3, 8, 14]. Nevertheless, in cases of severe hPIV infections the consideration of ribavirin therapy is in accordance with current clinical guidelines [15].

The study, based on a retrospective analysis utilizing our CARV registry database, was aimed at analyzing the impact of ribavirin on various outcomes related to hPIV infections and to comprehensively delineate the associated risk factors for the development of LRTD and mortality in an immunocompromised cohort of allo-SCT recipients.

Patients and methods

Patients

All consecutive CARV respiratory infections diagnosed in adult (≥ 16 years) allo-SCT recipients between December, 2013 and June, 2023 were prospectively registered at the Hospital Clinic Universitari of València (HCUV) and at the Hospital Universitari i Politècnic la Fe in València (HLF) as described in detail elsewhere [16, 17]. For the study purpose we included consecutive allo-SCT recipients with microbiologically documented hPIV infection. The registry started in 2013 and was retrospectively approved by the local ethics committee and the Spanish Agency of Medicines and Health products with reference code INC-RIB-2016-01. Further amendment which included the waiver of signed informed consent was also approved by the same local ethics committee in 2019 with the reference code 2019/351.

Treatment and supportive care

According to our treatment algorithm for respiratory syncytial virus (RSV) and hPIV set in December 2013 [18], ribavirin for hPIV infection was suggested only in patients with URTD at high risk of severe infection or progression to LRTD according to the ECIL-4 recommendation [15] and in those with high immunodeficiency scoring index (ISI) [19] and in all cases of LRTD, unless the respiratory symptoms improved or resolved at the time of microbiological results. However, given the weakness of scientific evidence for such a recommendation, the decision whether to treat was made by the treating physician. Briefly, oral or intravenous ribavirin was given at a loading dose of 200 mg every 8 h on day 1, 400 mg every 8 h on day 2, 600 mg every 8 h on day 3, and 800 mg every 8 h (maximum daily dose of 30 mg/kg) thereafter until the clinical symptoms resolved. Routine treatment with intravenous immunoglobulins (0.4 g/kg) were not given but prophylactic supply was administered in recipients with IgG serum levels were below 300 mg/dl.

Technical and diagnostic considerations

Nasopharyngeal aspirates, nasal swabs or induced sputa were collected from patients presenting with URTD and/or LRTD symptoms. Patients with radiological evidence of LRTD underwent bronchoalveolar lavage (BAL) whenever possible. At the HCUV, samples were subjected to PCR testing using the Luminex xTAG RVP Fast v1 assay developed by Luminex Molecular Diagnostics in Toronto, ON, Canada. Meanwhile, at the HLF, the CLART® PneumoVir DNA array assay by Genomica in Coslada, Spain was employed. Starting from July 2018, HLF adopted the BioFire FilmArray® Respiratory Panel by BioFire Diagnostics, a subsidiary of bioMérieux, located in Salt Lake City, UT. CARVs and bacteria targeted by these commercial multiplex PCR tests have been previously described in detail elsewhere [17, 18].

Definitions

URTD was defined by the combination of URT symptoms (rhinorrhea, sinusitis, otitis, or pharyngitis) and a positive

PCR test, but the absence of LRT symptoms and/or any indication of pulmonary infiltrates in the radiology results by chest X-ray or computed tomography (CT) scan.

We classified LRTD as possible or proven as previously described [20]. Possible LRTDs were defined as the detection of hPIV in a nasopharyngeal or sputum sample taken from patients showing clinical symptoms of tracheitis, bronchitis, bronchiolitis, or pneumonia (new onset of cough, rales, wheezing, cough-related chest pain, shortness of breath, dyspnea, or hypoxia) with new pulmonary infiltrates (but without confirmation of their presence in the lower respiratory tract). Proven LRTDs were defined when the abovementioned clinical-radiological features were accompanied by isolation of viral DNA/RNA in the BAL.

Co-infection was defined as a significant co-pathogen detected in concurrent nasopharyngeal or BAL that required antimicrobial intervention during hPIV infection and until its clinical and/or microbiological resolution. Co-infections also included the detection of other CARV in the same sample as that of hPIV.

Immunodeficiency scoring index (ISI) was calculated at the time of hPIV detection as previously described [19].

Ribavirin therapy at the URTD stage was considered when the drug was started in recipients without LRTD symptoms and at least 48 h before the radiological proof of pulmonary involvement. We categorized those who received ribavirin at the LRTD stage as part of the comparator (non-treated) group for purpose of the analysis. These individuals had not received ribavirin during the URTD stage and were considered as a progression to LRTD. In addition, the non-treatment group also comprises individuals who started ribavirin treatment on the same day or within 24 h prior to the onset of LRTD symptoms and/or radiological confirmation of LRTD involvement.

Statistical analysis

The primary endpoint was to compare the outcomes of patients who received ribavirin therapy versus those who did not. The secondary endpoint was to assess conditions associated with LRTD progression and all-cause mortality at day + 100 after hPIV detection. The main patient characteristics were reported by descriptive statistics on the total available information: medians and ranges were used for continuous variables, while absolute and percentage frequencies were used for categorical variables. For comparisons between antiviral cohorts Fisher exact test, Mann–Whitney's *U* test or median test was used when appropriate. Univariate and multivariate analyses of risk factors for hPIV-LRTD were calculated using logistic regression models. In recipients with LRTD, the survival analysis was performed using the Cox regression model and including ribavirin therapy as a time-dependent co-variate. A p value < 0.05 was considered statistically significant. All p values are two sided. Analyses were performed using the statistical software SPSS v. 25 (IBM SPSS Statistics, Armonk, New York, USA).

Results

Patient characteristics

A total of 230 consecutive allo-SCT recipients were included in the study. Table 1 provides comprehensive characteristics of the cohort, divided into those who received ribavirin treatment ($n = 61$, 27%) and those who did not ($n = 169$, 73%). The median age at allo-SCT was 52 years. There were no significant differences in patient characteristics between the treated and untreated groups. The study covered a long period (11 years) in the era of molecular diagnosis. The distribution of patients across the risk categories of ISI showed a trend to a higher proportion of high-risk patients in the treated group. The median time from allo-SCT to the first hPIV episode was shorter in the treated group. The proportion of hPIV LRTD was significantly different between the treated and untreated groups, with more proven cases in the treated group (28% vs 8%, $p < 0.001$). However, there were no significant differences in all-cause mortality and infectious mortality at day + 100 after hPIV infection between the treated and untreated groups. The median time from hPIV infection to death was similar across both groups. The follow-up duration for survivors after hPIV (median of 860 days for the whole cohort, range 30–3259 days) was also comparable among groups.

Clinical and biological characteristics of hPIV infection

Table 2 provides a detailed description of the characteristics and outcomes of patients categorized into those with only URTD, possible LRTD, and proven LRTD. The presence of URTD was observed in 229 out of 230 recipients (99.5%) and all recipients developing LRTD started with URT symptoms. Median time from URT symptoms onset to LRT symptoms onset and/or radiological proof of LRTD was 5 days (range 1–40 days) in those with proven LRTD and 7 days (range 0–80 days) in possible LRTD cases. The median age at allo-SCT was consistent across URTD, possible LRTD, and proven LRTD groups. The use of anti-thymocyte globulin (ATG) as part of conditioning was significantly higher in the LRTD groups. The distribution of ISI categories significantly differs between the groups with higher rate of moderate and severe ISI in

Table 1 Patient and transplant characteristics

Characteristics	Whole cohort ($n=230$)	Not treated* ($n=169$)	Treated with ribavirin* ($n=61$)	p value*
Age at allo-SCT (years), median (range)	52 (16–71)	52 (16–71)	52 (18–71)	0.8
Male, *n* (%)	123 (54)	89 (53)	34 (56)	0.4
Underlying malignancies, *n* (%)				0.21
AL/MDS/MPN	121 (53)/23(10)/9 (4)	93 (55)/15 (9)/6 (3.4)	28 (46)/8 (13)/3 (5)	
Chronic myeloid leukemia	5 (2)	4 (2)	1 (2)	
Lymphoid disorders	58 (25)	39 (23)	19 (31)	
Plasma cell disorders	13 (5.5)	11 (7)	2 (3)	
Others	1 (0.5)	1 (0.6)	0	
Prior Autologous-SCT, *n* (%)	53 (23)	39 (23)	14 (23)	0.99
Period of transplant, *n* (%)				0.5
≥ 2020	16 (7)	12 (7)	4 (7)	
2017–2019	110 (48)	78 (46)	32 (52)	
2014–2016	64 (28)	46 (27)	18 (29)	
< 2014	40 (17)	33 (20)	7 (12)	
Conditioning regimen, *n* (%)				0.64
RIC	140 (61)	101 (60)	39 (64)	
MAC	90 (39)	68 (40)	22 (36)	
Type of donor, *n* (%)				0.2
HLA-identical sibling	70 (30)	54 (32)	16 (26)	
HLA-identical unrelated donor	65 (28)	46 (27)	19 (32)	
HLA mismatch unrelated donor	34 (15)	29 (17)	5 (8)	
Haploidentical family	59 (26)	38 (23)	21 (34)	
Other	2 (1)	2 (1)	0	
Stem cell source, *n* (%)				0.11
PB	196 (85)	139 (82)	57 (93)	
CB	27 (12)	24 (14)	3 (5)	
BM	7 (3)	6 (4)	1 (2)	
ATG as a part of conditioning regimen, *n* (%)	36 (16)	30 (18)	6 (10)	0.22
GvHD prophylaxis, *n* (%)				0.7
Tacrolimus and sirolimus	27 (12)	18 (11)	9 (15)	
Tacrolimus or CsA + MTX or MMF	101 (44)	74 (44)	27 (44)	
Post-Cy	102 (44)	77 (45)	25 (41)	
ISI, *n* (%)				0.06
Low risk (0–2 points)	97 (42)	76 (45)	21 (34)	
Moderate risk (3–6 points)	114 (50)	83 (49)	31 (51)	
High risk (7–12 points)	19 (8)	10 (6)	9 (15)	
Median time from allo-SCT to hPIV, days (range)	329 (− 4–5258)	364 (− 4–5258)	262 (0–2974)	0.097
IgG levels in mg/dL, median (range)	612 (4–2432)	665 (4–2432)	526 (4–1697)	0.047
IgG < 300 mg/dL, *n* (%)	21 (9)	12 (7)	9 (15)	0.11
IgG < 400 mg/dL, *n* (%)	49 (21)	29 (17)	20 (33)	0.017
hPIV LRTD				< 0.001
Possible	33 (16)	22 (13)	11 (18)	
Proven	30 (13)	13 (8)	17 (28)	
Time from allo-SCT to 1st hPIV episode (categories), *n* (%)				0.41
Until day + 180	69 (30)	47 (28)	22 (36)	
181–1 year	52 (23)	38 (22)	14 (23)	
> 1 years	109 (47)	84 (50)	25 (41)	
All-cause mortality at day + 100 after hPIV, *n* (%)	14 (6)	10 (6)	4 (6.5)	0.5
Infectious mortality, *n* (%)	9 (4)	6 (4)	3 (5)	0.9
Median time from hPIV to death, days (range)	56 (6–96)	53 (6–96)	46 (7–95)	0.3
Median F/U for survivors after hPIV, days (range)	860 (30–3259)	785 (30–3208)	1064 (31–3259)	0.2

Table 1 (continued)

Abbreviations: *allo-SCT* allogeneic hematopoietic stem cell transplantation, *AL* acute leukemia, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasm, *RIC* reduced intensity conditioning, *MAC* myeloablative conditioning, *PB* peripheral blood, *CB* umbilical cord blood, *BM* bone marrow, *HLA* human leucocyte antigen system, *ATG* anti-thymocyte globulin, *GvHD* graft versus host disease, *CsA* cyclosporine A, *MTX* methotrexate, *MMF* mycophenolate mophetil acid, *Post-Cy* post-transplant cyclophosphamide, *ISI* immunodeficiency scoring index, *hPIV* human parainfluenza virus, *LRTD* lower respiratory tract disease, *F/U* follow-up

recipients with LRTD. In fact, patients with lower absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) with different cut-off (ALC below 0.1×10^9/L, below 0.5×10^9/L and below $< 1 \times 10^9$/L), the use of corticosteroids and recent or pre-engraftment allo-SCT were significantly more prevalent in the LRTD groups. hPIV-3 was the most common type (overall 53%) in all groups, and ribavirin therapy was significantly more frequent in proven LRTD patients. Co-infections were observed in a significant proportion of patients (26%), without significant group differences. Regarding the severity, hospital admission, intensive care unit (ICU) admission, and the need for oxygen support were significantly higher in LRTD groups.

Clinical and biological characteristics according to ribavirin therapy

Ribavirin was given to 61 patients (27%), mostly orally ($n = 55$, 90%) while six patients received it i.v. (10%). Median time from respiratory symptoms onset to ribavirin therapy was 7 days (range 0–88). Recipients with only URTD started ribavirin at median of 7 days (range 0–60 days) whereas those with possible and proven LRTD started antiviral therapy at median of 5 days (range 2–49 days) and 13 days (range 1–88 days), respectively, ($p = 0.3$) after hPIV diagnosis. Table 3 presents data on the outcomes of hPIV infection and the use of ribavirin treatment in patients with URTD, possible and proven LRTD. We first compared relevant clinical characteristics and analyzed the effect of ribavirin on the risk of LRTD progression and other severity parameters in recipients who started ribavirin at the URTD stage as compared to those who did not. The ISI categories did not significantly differ between the two groups. Recipient who received ribavirin at the URTD stage showed lower rate of LRTD progression (9% for the ribavirin group vs 30% in the non-treatment group, $p = 0.011$). However, we did not find any significant differences regarding hospital admission, oxygen requirements and intensive care unit (ICU) admission. We next compared these items in recipients who received ribavirin at the LRTD stage (both, possible and proven) as compared to those who remained untreated. Again, both groups were comparable although there was a trend towards a higher incidence of oxygen support before treatment in the ribavirin-treated group (46% vs. 29%, $p = 0.1$). Day + 100 overall mortality was not statistically different between untreated or treated possible or proven LRTD groups (20% vs. 7%, $p = 0.1$) (Fig. 1A). When we limited the analysis to recipients with proven LRTD even when both cohorts were comparable in terms of ALC and distribution of ISI risk categories, day + 100 all-cause mortality was lower in the ribavirin group as compared to those untreated (6% vs 39%, $p = 0.03$) (Fig. 1B) although among the five untreated recipients who died, only two developed respiratory failure with hPIV as the sole identified microbiological agent in their BAL. Two other cases resulted in respiratory failure, one with a combination of hPIV, rhinovirus, and adenovirus detected in the BAL, and the other with influenza A virus, who had been administered oseltamivir. The remaining patient succumbed to respiratory failure due to *legionella pneumonia* and hPIV.

Lower respiratory tract disease and risk factors for progression

Overall, 63 out of 230 (27%) developed LRTD (14% possible and 13% proven). Table 4 presents the results of univariate and multivariate logistic regression analyses to identify variables associated with the development of LRTD. Multivariate analysis identified corticosteroids > 30 mg/d (OR 3.5, 95% C.I. 1.3–9.4, $p = 0.013$), fever at the time of hPIV detection (OR 3.89, 95% C.I. 1.84–8.2, $p < 0.001$), ALC $< 0.2 \times 10^9$/L (OR 4.1, 95% C.I. 1.42–11.9, $p = 0.009$) and ALC $0.21–0.5 \times 10^9$/L (OR 2.6, 95% C.I. 1.01–7.3, $p = 0.05$) as independent risk factors for LRTD following allo-SCT. In contrast, ribavirin therapy showed a protective effect against LRTD progression (OR 0.19, 95% C.I. 0.05–0.75, $p = 0.018$).

Overall mortality, lower respiratory tract disease mortality and risk factors

Fourteen recipients (6%) died at day + 100 after hPIV detection, 9 of them (64%) due to hPIV with or without co-infections, two due to graft-versus-host disease (GvHD) and infections and three due to disease relapse. The mortality was higher for those with LRTD (17%) (possible 9% and proven 20% vs 3% in those with only URTD, $p < 0.001$). The mortality rate in those who were admitted to the hospital was 15%. Univariate and multivariate cox regression analyses for risk factors of day + 100 overall mortality in those with

Table 2 Clinical and biological characteristics of hPIV infection episodes in allo-SCT recipients according to upper or lower respiratory tract involvement

	Only URTD ($n=167$)	Possible LRTD ($n=33$)	Proven LRTD ($n=30$)	P-value
Transplant characteristics				
Age at allo-SCT (years), median (range)	52 (16–71)	52 (22–69)	52 (18–71)	0.8
ATG as part of conditioning, *n* (%)	20 (12)	8 (24)	8 (26)	0.043
GvHD prophylaxis, *n* (%)				0.9
Tacrolimus and sirolimus	21 (12)	4 (12)	2 (6)	
Tacrolimus or CsA + MTX or MMF	73 (44)	14 (43)	15 (49)	
Post-Cy	73 (44)	15 (45)	14 (45)	
Type of donor, n (%)				0.28
HLA-identical sibling	54 (33)	8 (24)	8 (27)	
HLA-identical unrelated donor	47 (28)	7 (21)	11 (35)	
HLA mismatch unrelated donor	19 (11)	8 (24)	7 (24)	
Haploidentical family	45 (27)	10 (31)	4 (14)	
Other	2 (1)	0	0	
Immunodeficiency Scoring Index, n (%) ‡				
ANC $< 0.5 \times 10^9$/L	5 (3)	2 (6)	5 (16)	0.009
ALC $< 0.2 \times 10^9$/L	7 (4)	6 (18)	9 (29)	< 0.001
Age ≥ 40 years	129 (77)	28 (84)	24 (77)	0.6
Myeloablative conditioning regimen	49 (29)	12 (36)	17 (55)	0.025
Corticosteroids	34 (20)	9 (27)	18 (58)	< 0.001
Recent or pre-engraftment allo-SCT	4 (2)	3 (9)	4 (14)	0.016
Active GvHD	73 (43)	17 (52)	20 (67)	0.06
ISI, n (%)				< 0.001
Low risk (0–2)	80 (48)	14 (43)	3 (10)	
Moderate risk (3–6)	81 (48)	13 (39)	20 (66)	
High risk (7–12)	6 (4)	6 (18)	7 (24)	
Other characteristics ‡				
On IS, *n* (%)	103 (62)	25 (76)	25 (83)	0.033
ALC $< 0.1 \times 10^9$/L, *n* (%)	4 (2)	4 (12)	6 (20)	< 0.001
ALC $< 0.5 \times 10^9$/L, *n* (%)	23 (14)	14 (42)	12 (40)	< 0.001
ALC $< 1 \times 10^9$/L, *n* (%)	56 (34)	21 (63)	19 (63)	< 0.001
IgG < 300 mg/dL	13 (8)	6 (18)	2 (7)	0.14
IgG < 400 mg/dL	34 (20)	8 (24)	8 (23)	0.5
RVI characteristics and clinical consequences				
hPIV type, *n* (%)				0.4
1	23 (14)	3 (9)	0	
2	19 (11)	4 (12)	3 (10)	
3	95 (57)	22 (67)	22 (73)	
4	30 (18)	4 (12)	5 (17)	
Ribavirin therapy, n (%)	33 (20)	11 (33)	17 (55)	< 0.001
Respiratory co-infections, n (%)	43 (26)	11 (33)	11 (37)	0.7
Other CARVs	38 (23)	9 (27)	9 (30)	
Bacterial	3 (2)	1 (3)	1 (3)	
Fungal	2 (1)	1 (3)	1 (3)	
Hospital admission, *n* (%)	16 (10)	22 (67)	27 (90)	< 0.001
ICU admission, *n* (%)	1 (0.5)	2 (6)	6 (20)	< 0.001
Oxygen support, *n* (%)	3 (2)	4 (12)	19 (63)	< 0.001
Day + 100 overall mortality, *n* (%)	5 (3)	3 (9)	6 (20)	< 0.001

Abbreviations: *URTD* upper respiratory tract disease, *LRTD* lower respiratory tract disease, *Allo-SCT* allogeneic hematopoietic stem cell transplantation, *ATG* anti-thymocyte globulin, *GvHD* graft-versus-host disease, *CsA* cyclosporine A, *MTX* methotrexate, *MMF* mycophenolate mophetil acid, *Post-Cy* post-transplant cyclophosphamide, *HLA* human leukocyte antigen, *hPIV* human parainfluenza virus, *ANC* absolute neutrophil count, *ALC* absolute lymphocyte count, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *ISI* immunodeficiency scoring index, *RVI* respiratory virus infection, *IS* immunosuppressants, *CARVs* community acquired respiratory virus, *ICU* intensive care unit, *IgG* immunoglobulin level

‡All variables were captured at the time of hPIV diagnosis

Table 3 Ribavirin effect on progression to LRTD and on overall mortality in those with possible and/or proven LRTD

Respiratory co-infections	Ribavirin	Untreated	*p* value
URTD at the time of RbV	(*n* = 33)	(*n* = 197)	
ISI, *n* (%)			0.8
Low risk (0–2)	15 (45)	82 (42)	
Moderate risk (3–6)	16 (48)	98 (50)	
High risk (7–12)	2 (7)	17 (8)	
ALC < 0.1×10^9/L, *n* (%)	2 (6)	12 (6)	0.99
ALC < 0.5×10^9/L, *n* (%)	5 (15)	44 (22)	0.49
ALC < 1×10^9/L, *n* (%)	13 (39)	83 (42)	0.8
Corticosteroids, *n* (%)	7 (21)	54 (27)	0.52
Active GvHD, *n* (%)	18 (54)	92 (47)	0.45
Period of transplant, *n* (%)			0.053
≥ 2020	1 (3)	16 (7)	
2017–2019	12 (36)	97 (49)	
2014–2016	16 (49)	49 (25)	
< 2014	4 (12)	35 (19)	
Progression to LRTD, *n* (%)	3 (9)	60 (30)	0.011
ICU, *N* (%)	0	9 (7)	0.3
Hospital admission, *n* (%)	7 (21)	58 (29)	0.4
Oxygen support, *n* (%)	1 (3)	25 (13)	0.1
Day + 100 overall mortality, *n* (%)	3 (9)	11 (6)	0.43
Possible and Proven LRTD	(*n* = 28)	(*n* = 35)	
ISI, *n* (%)			0.59
Low risk (0–2)	6 (22)	11 (31)	
Moderate risk (3–6)	15 (53)	18 (52)	
High risk (7–12)	7 (25)	6 (17)	
ALC < 0.1×10^9/L, *n* (%)	7 (25)	3 (9)	0.09
ALC < 0.5×10^9/L, *n* (%)	13 (46)	13 (37)	0.6
ALC < 1×10^9/L, *n* (%)	16 (57)	24 (68)	0.43
Corticosteroids, *n* (%)	16 (57)	20 (57)	0.99
Active GvHD, *n* (%)	14 (50)	19 (54)	0.99
Co-infections, *n* (%)	7 (25)	15 (42)	0.2
Period of transplant, *n* (%)			0.015
≥ 2020	3 (11)	1 (3)	
2017–2019	20 (70)	14 (40)	
2014–2016	2 (8)	7 (20)	
< 2014	3 (11)	13 (37)	
Hospital admission, *n* (%)	24 (86)	25 (71)	0.22
Oxygen support, *n* (%)	13 (46)	10 (29)	0.1
ICU, *n* (%)	2 (7)	6 (17)	0.2
Day + 100 overall mortality, *n* (%)	2 (7)	7 (20)	0.12
Proven LRTD	(*n* = 17)	(*n* = 13)	
ISI, n (%)			0.09
Low risk (0–2)	0	3 (23)	
Moderate risk (3–6)	12 (70)	8 (62)	
High risk (7–12)	5 (30)	2 (15)	
ALC < 0.1 × 109/L, *n* (%)	5 (30)	1 (8)	0.1
ALC < 0.5 × 109/L, *n* (%)	7 (41)	5 (38)	0.99
ALC < 1 × 109/L, *n* (%)	9 (53)	10 (77)	0.25
Corticosteroids, *n* (%)	10 (59)	8 (62)	0.99
Active GvHD, *n* (%)	11 (65)	9 (69)	0.99
Co-infections, *n* (%)	6 (35)	5 (38)	0.99
Period of transplant, *n* (%)			0.025
≥ 2020	2 (12)	0	
2017–2019	12 (70)	5 (39)	
2014–2016	2 (12)	1 (7)	
< 2014	1 (6)	7 (54)	
Hospital admission, *n* (%)	16 (94)	11 (85)	0.56
Oxygen support, *n* (%)	11 (65)	8 (62)	0.99
ICU, *n* (%)	1 (6)	5 (39)	0.03
Day + 100 overall mortality, *n* (%)	1 (6)	5 (39)	0.03

Abbreviations: *URTD* upper respiratory tract disease, *LRTD* lower respiratory tract disease, *RbV* ribavirin, *GvHD* graft-versus-host disease, *ALC* absolute lymphocyte count, *ISI* immunodeficiency scoring index, *ICU* intensive care unit

possible or proven LRTD is shown in Table 4. Multivariate analysis identified co-infections [Hazard ratio (HR) 5.7, 95% C.I. 1.4–23.5, $p = 0.015$], and ALC below 0.2×10^9/L (HR 17.7, 95% C.I. 3.6–87.1, $p < 0.001$) as conditions independently associated with higher mortality.

Discussion

The present study offers new insights into hPIV infection following allo-SCT in the molecular diagnostics era. A key finding is the potential benefit of ribavirin therapy in reducing the progression to LRTD. We also identified specific risk factors associated with an increased risk of LRTD; low ALC, fever, and use of higher doses of corticosteroids. Low ALC and co-infections were independently linked to higher day + 100 all-cause mortality.

It is well-known that hPIV infection tends to be more severe in SCT recipients than in the general population, with allo-SCT recipients displaying higher viral loads in respiratory samples [21]. In our cohort, we observed a relatively high rate of LRTD (27%), consistent with findings from a previous meta-analysis (37%) [9] and a recent single-center cohort study (47%) [22]. The overall mortality in our cohort was 6%, but those with LRTD exhibited a higher mortality rate of 17%, in line with prior experiences [1, 10, 23]. However, our study reported a somewhat lower overall mortality than previously reported (12% overall and 27% in those with LRTD) [9] which may be in part explained by the prospective nature of our registry enabling us to capture most of mild cases. Still, this data underlay the need of effective vaccines and/or antiviral drugs developments in this setting.

In this sense, ribavirin emerged as the only widely available antiviral drug that has demonstrated some efficacy

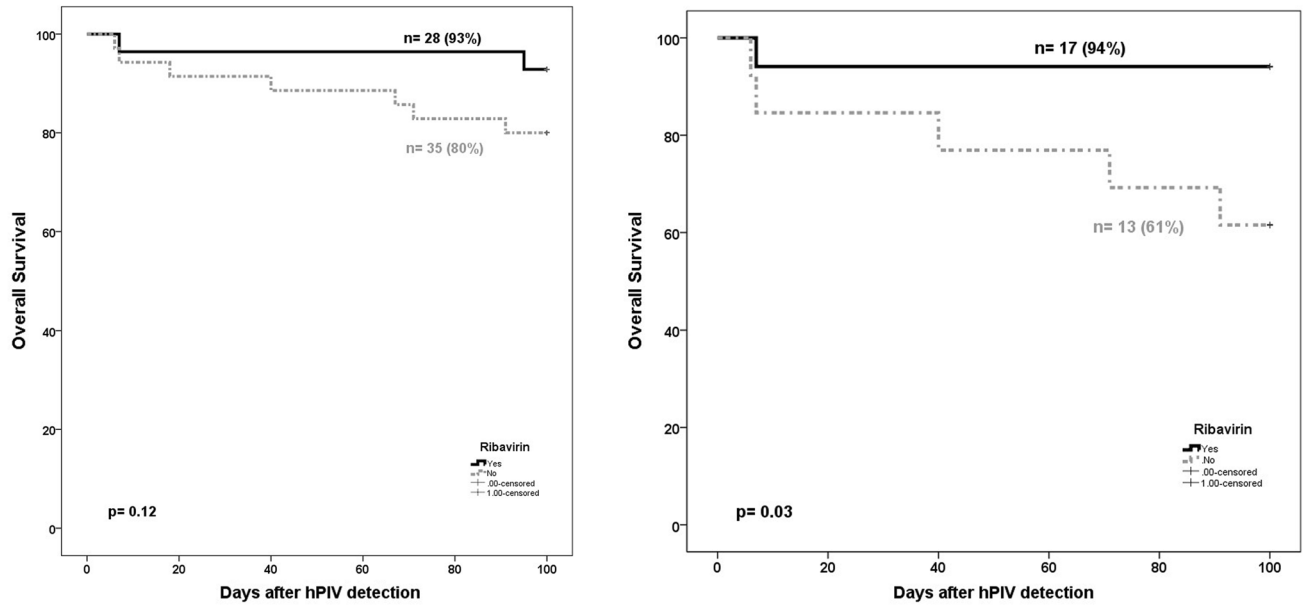

Fig. 1 **A**, **B** Overall survival at day + 100 after hPIV detection according to ribavirin therapy **A** in those with possible and proven LRTD and **B** in those with only proven LRTD

in vitro against hPIV [24], but extensive case series presented more than 15 years ago and before the PCR era have revealed that ribavirin lacks a significant impact on viral shedding, symptom duration, progression to LRTD, and mortality in SCT recipients [14, 25]. It's important to note that in most of these studies, ribavirin was administered to severe cases making comparisons between treated and not treated potentially biased [9]. Thus, its benefit in treating hPIV infections in allo-SCT recipients remains a matter of debate. While our approach recommended treating high-risk recipients with ribavirin [18], the limited supporting evidence placed the ultimate decision in the hands of the attending physician. Several physicians chose not to pursue ribavirin treatment due to the dearth of scientific data regarding its benefits, as well as concerns about its potential toxicity and the risk of drug-to-drug interactions. These circumstances resulted in a reasonably balanced distribution of well-established severity risk factors among both, treated and untreated patients, making our series particularly suitable for comparative analyses.

In our cohort, we observed a significant advantage in using ribavirin therapy to reduce the progression to LRTD when administered during the URTD stage. Specifically, the LRTD rate was 9% in the treated group compared to 30% in those who did not received ribavirin at the URTD stage. Notably, almost half of the treated cohort (28 out of 61, or 46%) received ribavirin at the LRTD stage. Although in patients with proven LRTD, ribavirin showed higher day + 100 survival a (94% vs. 61%, $p = 0.03$) we did not find significant differences in all-cause mortality and infectious mortality at day + 100 after hPIV infection between the treated and untreated groups. In fact, 3 out of 5 deaths in the untreated patient group had co-infections which limited our ability to draw conclusions. It is likely that the limited number of events ($n = 9$) in those with LRTD may have limited our ability to find a significant benefit in multivariate analysis emphasizing that larger cohorts could be required to specifically address this issue. The potential benefit of ribavirin therapy for hPIV is also supported by a recent retrospective report in lung transplant recipients with pneumoviridae and paramyxoviridae viruses (RSV, hMPV and hPIV) infections where ribavirin treatment was associated with better long-term recovery of FEV1 post infection and lower chronic lung allograft dysfunction as compared to no ribavirin, in particular in cases of hPIV LRTD [27]. Another recent retrospective report in allo-SCT with RSV or hPIV LRTD (all treated with oral ribavirin) showed a mortality rate of 11% [27] which is comparable to that observed in our series in ribavirin treated recipients with possible or proven LRTD (7%). Although we were not able to analyze the effect of different ribavirin formulations in the current series, previous encounters with alternative ribavirin formulations, rather than the aerosolized variant, have demonstrated similar efficacy in addressing RSV infections in allo-SCT [28]. Consequently, it appears that the method of ribavirin administration does not significantly influence its effectiveness. Although there are other molecules in development for hPIV (DAS181 a sialidase fusion protein fludase) [29], ribavirin is widely available in most centers/countries and deserve to be explored in a prospective randomized clinical trial.

Table 4 Univariate and multivariate analysis of risk factors for hPIV lower respiratory tract disease (LRTD) and overall mortality

Variables	Log. Regr. LRTD ($n=230$)				Cox. Regr. Day + 100 Overall mortality in those with LRTD ($n=63$)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% C.I.) % (95%C.I.)	*p*	OR (95% C.I.)	*p*	HR (95% C.I.) % (95%C.I.)	*p* value	HR (95% C.I.) (95%C.I.)	*p* value
Patient CMV serology								
Positive	0.8 (0.41–1.58)	0.53			2.8 (0.35–22.4)	0.33		
Negative	1				1			
Donor/recipient Sex mismatch								
Female to male	1.2 (0.57–2.58)	0.6			0.5 (0.06–4)	0.51		
Others	1				1			
Gender								
Male	1				1			
Female	0.97 (0.54–1.74)	0.92			1.46 (0.39–5.4)	0.57		
HLA mismatch	1.3 (0.73–2.34)	0.37			1.53 (0.41–5.7)	0.52		
ATG as a part of conditioning	2.5 (1.2–5.2)	0.014			2.6 (0.7–9.7)	0.15	ns	
GVHD prophylaxis								
Sir-Tac	1				1			
Post-Cy	1.39 (0.5–3.79)	0.52			0.75 (0.07–5.8)	0.9		
Others	1.34 (0.49–3.6)	0.56			2.1 (0.34–7.3)	0.32		
Corticosteroids *	2.89 (1.54–5.4)	0.001	NT		1.7 (0.45–6.3)	0.42	NT	
Corticosteroids dose								
No	1		1		1			
< 30 mg/d	1.76 (0.78–3.9)	0.16	1.52 (0.6–3.6)	0.3	0.77 (0.08–6.9)	0.81		
≥ 30 mg/d	5.3 (2.29–12.5)	< 0.001	3.5 (1.3–9.4)	0.013	2.44 (0.6–9.7)	0.2		
On IS	2.39 (1.2–4.74)	0.013	ns		2.2 (0.27–17.6)	0.45	ns	
ALC < 0.5 × 109/L	4.33 (2.2–8.4)	< 0.001	NT		5.56 (1.15–26.8)	0.032	NT	
ALC < 0.2 × 109/L*	7.1 (2.7–18.3)	< 0.001	NT		14.1 (2.9–68.5)	0.001	17.7 (3.6–87.1)	< 0.001
ALC < 0.1 × 109/L	7.59 (2.28–25)	0.001	NT		3 (0.75–12)	0.12	NT	
ALC < 1 × 109/L	3.4 (1.84–6.2)	< 0.001	NT		4.9 (0.61–39.25)	0.13	NT	
ALC categories							NT	
< 0.2 × 109/L	8.8 (3.3–23.4)	< 0.001	4.1 (1.42–11.9)	0.009	13.4 (1.6–109)	0.015		
0.2–0.5 × 109/L	3.5 (1.4–8.5)	0.007	2.6 (1.01–7.3)	0.05	1.9 (0.03–15)	0.9		
0.51–1 × 109/L	2 (0.94–4.3)	0.07	1.58 (0.68–3.6)	0.28	1.6 (0.10–26.8)	0.7		
> 1 × 109/L	1		1		1			
ANC < 0.5 × 109/L*	4 (1.22–13.11)	0.022	NT		1 (0.13–8.3)	0.94		
Age ≥ 40 years*	1.39 (0.66–2.9)	0.38	NT		1.6 (0.2–13.2)	0.63		
Active GvHD at the time RVI*	1.82 (1.01–3.3)	0.043	NT		0.86 (0.23–3.2)	0.82		
Periengraftment*	5.1 (1.4–18)	0.012	NT		2.5 (0.52–12.2)	0.24		
IgG < 300 mg/dL	2.04 (0.79–5.24)	0.13	ns		1.1 (0.3–1.6)	0.9		
IgG < 400 mg/dL	1.49 (0.73–3.03)	0.27			1.69 (0.4–7)	0.46		
Time from allo-SCT to 1st hPIV episode								
≤ 180 days	1.8 (0.92–3.4)	0.086	ns		3.3 (0.67–16.4)	0.14	ns	
181–365 days	1.2 (0.58–2.64)	0.58			0.88 (0.08–9.7)	0.9		
> 365 days	1				1			
Myeloablative*	1.96 (1.06–3.6)	0.03	NT		0.86 (0.23–3.2)	0.84		
Period of transplant			ns					
≥ 2020	0.5 (0.13–1.8)	0.29			Not calculable			
2017–2019	0.67 (0.31–1.4)	0.6			0.42 (0.1–1.7)	0.22		

Table 4 (continued)

Variables	Log. Regr. LRTD ($n=230$)				Cox. Regr. Day + 100 Overall mortality in those with LRTD ($n=63$)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% C.I.) % (95%C.I.)	*p*	OR (95% C.I.)	*p*	HR (95% C.I.) % (95%C.I.)	*p* value	HR (95% C.I.) (95%C.I.)	*p* value
2014–2016	0.24 (0.09–0.63)	0.04			0.4 (0.04–3.5)	0.41		
< 2014	1				1			
hPIV subtype								
1	1				1			
2	2.8 (0.6–12.4)	0.17			0.34 (0.02–5.5)	0.45		
3	3.55 (1.01–12.4)	0.048	ns		0.29 (0.03–2.5)	0.26		
4	2.3 (0.55–9.4)	0.25			0.58 (0.05–6.4)	0.66		
Ribavirin therapy	NT				0.3 (0.06–1.4)	0.1	ns	
Ribavirin at the URTD stage	0.22 (0.06–0.77)	0.018	0.19 (0.05–0.75)	0.018			NT	
Co-infections	NT				4.17 (1.04–16.7)	0.043	5.7 (1.4–23.5)	0.015
Fever at the time of hPIV	4.97 (2.4–9.9)	< 0.001	3.89 (1.84–8.2)	< 0.001	2.6 (0.33–21.1)	0.35		
ISI**			ns				ns	
Low risk (0–2)	1				1			
Moderate risk (3–6)	1.97 (0.99–3.71)	0.054			0.5 (0.07–3.6)	0.51		
High risk (7–12)	10.2 (3.39–30.6)	< 0.001			3.63 (0.7–18.7)	0.1		

For LRTD multivariate analysis, we found moderate ISI (OR 1.72, 95% C.I. 0.86–3.46, $p=0.12$) and high-risk ISI (OR 5.9, 95% C.I. 1.84–19.2, $p=0.003$)

For day + 90 overall mortality multivariate analysis we found moderate ISI (HR 0.32, 95% C.I. 0.04–2.4, $p=0.27$) and high-risk ISI (HR 3.2, 95% C.I. 0.6–16.7, $p=0.16$) after removing ALC < 0.2 from the multivariate model

Abbreviations: *C.I.* confidence interval, *Log. Regr* Logistic regression model, *OR* Odds Ratio, *IFD* invasive pulmonary fungal disease, *ATG* anti-thymocyte globulin, *Sir* sirolimus, *Tac* tacrolimus, *CsA* cyclosporine A, *MTX* methotrexate, *Post-Cy* post-transplant cyclophosphamide, *PDN* prednisone, *CARV LRTD* community-acquired respiratory virus lower respiratory tract disease, *GvHD* graft-versus-host disease, *IgG* immunoglobulin level, *Allo-SCT* allogeneic hematopoietic stem cell transplantation, *ISI* immunodeficiency score index, *ANC* absolute neutrophil count, *ALC* absolute lymphocyte count, *ns* not significant, *NT* not tested

*These variables were included in the ISI score and thus were not included in the multivariate model

**The ISI variable was significant in multivariate analyses if ALC categories were not included into the final model (see text)

Regarding risk factors for progression to LRTD and in accordance with prior data lymphopenia [10, 11] and the use of corticosteroids [4, 22] were the main factors associated with LRTD progression supporting the chief role of T cell lymphocyte function in particular CD4 + and CD8 + hPIV-specific T cells, in controlling and clearing the virus in allo-SCT recipients [30]. A clinical parameter that has not been identified yet as a risk factor for developing hPIV LRTD was the presence of fever at the time of virus detection. Fever has been associated with LRTD in allo-SCT recipients with common seasonal hCoV [31]. This finding is relevant since it supports that recipients who develop fever in the context of a CARV should undergo a detailed radiological study, preferable through chest computerized tomography. In addition, if pulmonary abnormality were detected in radiology studies, a BAL is highly recommended since proven hPIV LRTD showed the highest mortality rate [20]. Other risk factors for mortality in our series included lymphopenia, in particular ALC $< 0.2 \times 10^9$/L, and co-infections. Both have been already associated with higher mortality in allo-SCT recipients with hPIV in other series [10, 23]. It is well-known that CARV favorize bacterial and fungal co-infections as recently reviewed [13]. Thus, co-infections should be actively rule out and treated aggressively in this context to overcome its deleterious effect in these patients.

We acknowledge certain limitations in our present study, including the non-randomized design, variations in PCR testing methods, and differing criteria for ribavirin usage. Nonetheless, the strengths of this registry lie registering all consecutive episodes including mild cases and the well-balanced characteristics observed between treated and untreated cohorts.

Conclusions

Ribavirin therapy demonstrates a benefit in reducing the LRTD progression. Low ALC as well as fever and corticosteroid > 30 mg/d increased risk of LRTD progression. Additionally, higher mortality rates were associated with lower ALC and co-infections.

Author contributions Authors responsible for the conception and the design of the study: Jose Luis Piñana and Ariadna Perez. Authors who performed the data analysis and generated the tables and figures: Jose Luis Piñana and Per Ljungman. Authors responsible for patient recruitment: José Luis Piñana, Juan Montoro, Ariadna Pérez, Pedro Chorão, Dolores Gómez, Manuel Guerreiro, Marta Villalba, and Rafael Hernani. Authors responsible for writing the manuscript: Jose Luis Piñana, Ariadna Perez, Per Ljungman, David Navarro, Dolores Gomez, Estela Gimenez and Carlos Solano were responsible for writing and supervising the writing of the manuscript. All co-authors were responsible for reviewing the analysis interpretation, suggesting modifications to the text, critically reviewing the manuscript, and for the final approval of the manuscript.

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Declarations

Conflict of interest The author(s) declare that they have no conflicts of interest and have no funding resources to declare for this study.

Ethics approval statement The local research ethics committee of the Hospital Clínico Universitario of Valencia approved the registry and study protocol (reference code 2019/351).

Patient consent statement All patients included in this registry gave their signed informed consent in accordance with the declaration of Helsinki.

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