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Clinical Effectiveness of Influenza Vaccination After Allogeneic Hematopoietic Stem Cell Transplantation: A Cross-sectional, Prospective, Observational Study

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Background. Vaccination is the primary method for preventing influenza respiratory virus infection (RVI). Although the influenza vaccine is able to achieve serological responses in some allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients, its clinical benefits are still uncertain.

Methods. In this prospective, cross-sectional study, we retrospectively analyzed the effect of inactivated trivalent influenza vaccination on the prevalence of influenza RVI in a consecutive cohort of 136 allo-HSCT adult recipients who developed 161 RVI over 5 flu seasons (from 2013 to 2018). Respiratory viruses in upper– and/or lower–respiratory tract specimens were tested using multiplex polymerase chain reaction panel assays.

Results. Overall, we diagnosed 74 episodes (46%) of influenza RVI in 70 allo-HSCT recipients. Influenza RVI occurred in 51% of the non-vaccinated compared to 36% of the vaccinated recipients ($P = .036$). A multivariate analysis showed that influenza vaccination was associated with a lower prevalence of influenza RVI (odds ratio [OR] 0.39, $P = .01$). A multivariate risk factor analysis of lower–respiratory tract disease (LRTD) identified 2 conditions associated with the probability of influenza RVI progression: influenza vaccination (OR 0.12, 95% confidence interval [CI] 0.014–1, $P = .05$) and a high-risk immunodeficiency score (OR 36, 95% CI 2.26–575, $P = .011$). Influenza vaccination was also associated with a lower likelihood of an influenza-related hospital admission (14% vs 2%, $P = .04$).

Conclusions. This study shows that influenza vaccination may have a clinical benefit in allo-HSCT recipients with virologically-confirmed RVI, in terms of a lower influenza RVI prevalence, slower LRTD progression, and lower likelihood of hospital admission.

Keywords. community-acquired respiratory virus; influenza virus; allogeneic hematopoietic stem cell transplantation; inactivated trivalent influenza vaccine; immunodeficiency score index.

The influenza virus has a significant impact on morbidity and mortality in allogeneic hematopoietic stem cell transplantation patients (allo-HSCT), leading to complications ranging from self-limited upper–respiratory tract infections to life-threatening or fatal pneumonias [1–4]. The particular threat influenza poses for allo-HSCT recipients was well documented during the 2009 influenza A/H1N1 pandemic, as well as during consecutive seasonal influenza epidemics. It showed increased risks of subsequent bacterial pneumonia, hospital admissions, mechanical ventilation requirements, and mortality [5, 6].

Vaccination is the primary method for preventing influenza infections, but it is less effective in immunocompromised patients than in healthy individuals [7–10]. Based on studies analyzing serological responses, the inactivated influenza vaccine is strongly recommended annually for patients beyond 6 months post-transplant [11–14]; beyond 3 months after allo-HSCT if without graft-versus-host disease (GvHD) or immunosuppression [10]; or during community outbreaks [13, 15]. However, allo-HSCT recipients respond poorly to vaccinations: only one-third of allo-HSCT recipients will achieve protective influenza antibody titers [7, 9, 10], which obviously limits the efficacy of such a vaccine, challenging reports on its clinical benefits. In fact, clinical evidence of influenza-inactivated vaccine effectiveness after allo-HSCT is very limited [16]. Strategies based on an influenza vaccine with a higher antigen dose [17], multiple vaccine doses [18], or adjuvanted vaccines [19] might improve immune responses, although no controlled trials have been performed.

We conducted a prospective, cross-sectional, observational epidemiological study of community-acquired respiratory virus (CARV) respiratory tract disease (RTD) in allo-HSCT recipients who developed upper RTD (URTD) and/or lower RTD (LRTD) symptoms after transplant. Patients' influenza vaccination status

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was prospectively recorded at the time of their respiratory virus screening. In this study, we report the prevalence of influenza RTD according to the vaccination status over 5 consecutive influenza seasons in a consecutive series of allo-HSCT recipients with virologically-documented respiratory virus infections (RVIs).

PATIENTS AND METHODS

Study Population

This was a prospective, cross-sectional study of RVIs in adult (>18 years) allo-HSCT recipients that was conducted at 2 Spanish transplant centers. The whole cohort comprised consecutive allo-HSCT recipients with respiratory symptoms who were prospectively screened for respiratory viruses at the Hospital Clinic Universitari of Valencia (HCUV) between December 2013 and May 2016 and at the Hospital Universitari i Politècnic la Fe in Valencia (HLF) from June 2016 to May 2018.

Characteristics of the Respiratory Virus Survey Protocol

In December 2013 at the HCUV and in May 2016 at the HLF, we implemented the medical information/education for recipients and caregivers, explaining in detail the risks of having RVIs in the context of immunosuppression. The specific information provided included a description of the respiratory symptoms that merit urgent notification to the transplant team; recommendations concerning screening for respiratory viruses; details of available therapies; and infectious prevention control measures for patients and caregivers. A telephone number (on-call 24 h) for emergent conditions was also provided [20]. The local ethics committee approved the study protocol.

Clinical and Biological Variables

We prospectively recorded participants' clinical and biological characteristics at the time of CARV polymerase chain reaction (PCR) test screening, including the month and year of vaccination and the influenza vaccination status at each flu season. Variables included the immunodeficiency scoring index (ISI) [21] and Basel immunodeficiency grading [22, 23] results; hospital admissions; the use of immunosuppressant drugs; the presence of signs or symptoms of acute or chronic GvHD; and transplant characteristics.

Cohort Selection

With the aim of retrospectively comparing the influenza RTD prevalence between vaccinated and non-vaccinated participants, we included 1 recipient/RV episode/vaccination status in each flu season, following the selection algorithm described in Figure 1. We designed the case selection as follows: the first inclusion criterion was to retrospectively select all RVI episodes (irrespective of the CARVs detected) with known vaccination statuses. The next step was to divide the CARV episodes into 2 groups according to the vaccination status at each RVI episode (vaccinated or unvaccinated, in each corresponding flu season). Following recommendations from the World Health Organization's guidelines [24], we excluded the CARV episodes taking place outside the flu seasons (between June and

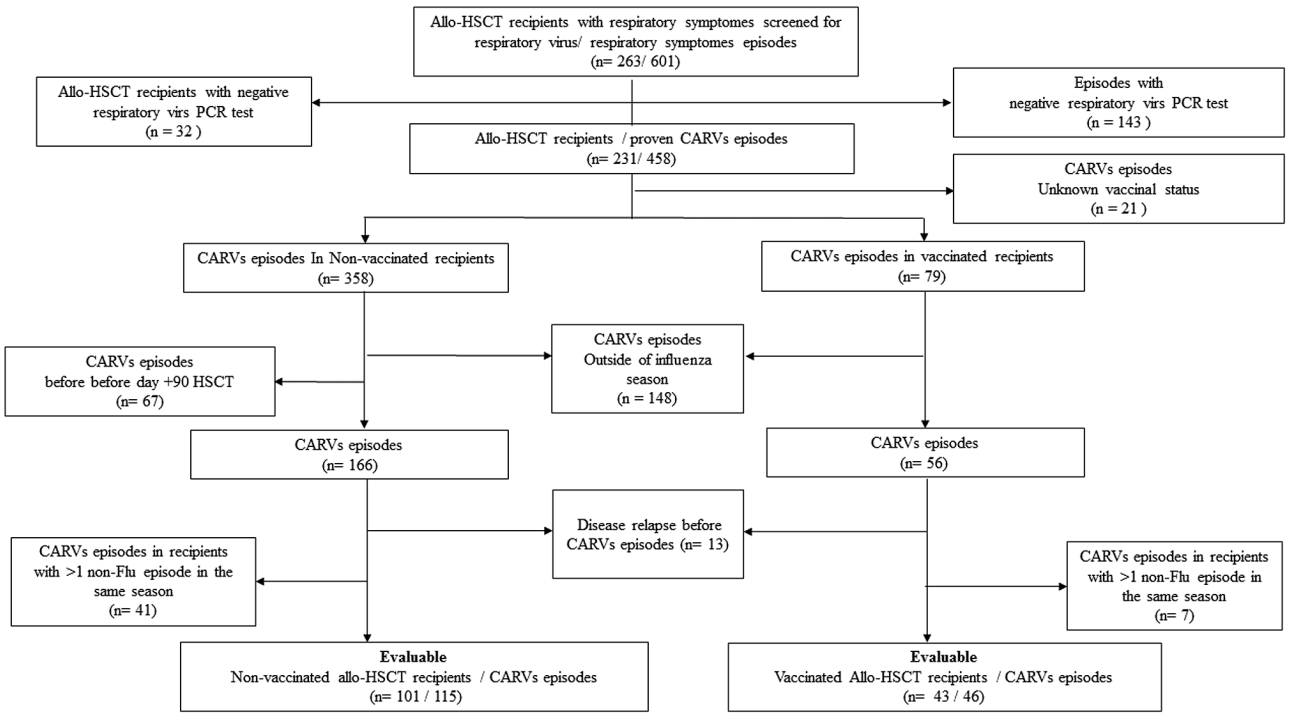

Figure 1. Study selection criteria algorithm. Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CARV, community-acquired respiratory virus; PCR, polymerase chain reaction; RVI, respiratory virus infection.

November) from both groups. We considered December to May as recruitment periods, according to our local and national epidemiological data, since influenza viruses were circulating in our community. The third step was to exclude episodes that occurred before day 90 after a stem cell infusion from the unvaccinated group, since the vaccine was not given to any recipients during that period and the first recorded influenza vaccine was given at day 91 after transplant. For both cohorts, we also excluded RVI episodes when baseline disease relapses occurred before the CARV episode. For recipients with more than 1 RVI episode in the same flu season, we applied the following criteria: recipients with more than 1 episode of CARV RVI other than influenza during the same flu season were computed only once and classed as not having an influenza infection in that season. Recipients with more than 1 episode of RVI and whose vaccination status changed between 2 consecutive CARV RVI episodes in the same season were computed twice: once in the non-vaccinated group and once (after vaccination) in the vaccinated group. If a recipient developed 2 RVI episodes caused by 2 different influenza viruses (ie, influenza A H1/N1 and B) at different time intervals during the same flu season, both episodes were computed in the corresponding group. When a recipient developed 2 influenza virus RVI episodes in the same season and the same influenza virus was detected, only the first episode was computed. Finally, when a recipient developed 2 RVI episodes, 1 of them caused by the influenza virus, we only computed the influenza episode in that season.

Vaccination Policy and Vaccine Composition

Annual influenza vaccination was recommended to all patients at both transplant centers after the third month following allo-HSCT. Recipients received a seasonal inactivate trivalent influenza vaccine according to the national health vaccination program that ran from November until February in each flu season. For patients with moderate to severe GvHD at the time of the vaccination program who had received gammaglobulin, anti-thymocytic globuline, or rituximab within the 3 months before the flu vaccine period, vaccine administration remained at the physician's discretion.

For the 2013–2014 flu season, the influenza inactivated trivalent vaccine covered the following influenza subtypes: A/California/7/2009 (H1N1)pdm09; A/Victoria/361/2011 (H3N2); and B/Massachusetts/2/2012 (Yamagata). For 2014–2015, it covered: A/California/7/2009 (H1N1)pdm09; A/Texas/50/2012 (H3N2); and B/Massachusetts/2/2012 (Yamagata). For 2015–2016, it covered: A/California/7/2009 (H1N1)pmd09; A/Switzerland/9715293/2013 (H3N2); and B/Phuket/3073/2013 (Yamagata). For 2016–2017, it covered: A/California/7/2009 (H1N1)pdm09; A/Hong Kong/4801/2014 (H3N2); and B/Brisbane/60/2008 (Victoria). Finally, for 2017–2018, it covered: A/Michigan/45/2015 (H1N1)pdm09; A/Hong Kong/4801/2014 (H3N2); and B/Brisbane/60/2008 (Victoria).

Definitions

URTD was defined as a combination of upper–respiratory tract symptoms (rhinorrhea, sinusitis, otitis, or pharyngitis), as well as the positive identification of a CARV by a PCR test and the absence of lower–respiratory tract infection symptoms and/or any indication of pulmonary infiltrates in chest X-ray or computed tomography (CT) scan radiology results. We classified LRTD as possible, probable, or confirmed, as previously described [25]. There were no probable episodes, because we did not perform bronchoscopies in patients without the radiological proof of pulmonary involvement. We defined episodes as an URTD or LRTD according to European Conference on Infections in Leukaemia–4 recommendations [26]. Acute GvHD was diagnosed and graded according to the standard criteria [27].

Technical and Diagnostic Considerations

Patients with URTD symptoms underwent nasopharyngeal aspiration, nasopharyngeal swabs, or an induced sputum test, while bronchoalveolar lavage (BAL) was performed in patients with a LRTD whenever possible. CARV testing in BAL samples were performed with 2 real-time PCR multiplex platforms, as described elsewhere in detail [28]. At the HCUV, samples were tested by real-time PCR using the Luminex xTAG RVP Fast v1 assay (Luminex Molecular Diagnostics, Toronto, Canada), while at HLF the CLART PneumoVir DNA array assay (Genomica, Coslada, Spain) was performed and interpreted following the manufacturer's recommendations. The CLART PneumoVir DNA array assay differs from the Luminex xTAG RVP Fast assay in that it detects influenza C virus, but not alphacoronavirus NL63 virus or betacoronaviruses HKU1 and OC43. The CLART PneumoVir identifies the new influenza A/H1N1v.

Endpoints and Statistical Analysis

The primary objective of the study was to compare the prevalence of influenza URTDs and/or LRTDs and clinical characteristics among vaccinated and unvaccinated allo-HSCT recipients. Secondary endpoints included identifying the risk factors for both influenza RTD and progression of the influenza virus from an URTD to a LRTD.

Frequencies were compared using the χ^2 test (Fisher exact test) for categorical variables. Differences between medians were compared using the Mann–Whitney U test. Univariate and multivariate analyses of the association of clinical and biological risk factors with the progression of influenza LRTD were calculated using logistic regression models. For multivariate analyses, only variables with parameter estimates showing a P value ≤ .10 in the univariate analysis were finally included. We reported 2-sided exact P values, and P values ≤ .05 were considered statistically significant. The data were analyzed with the SPSS (version 20.0) statistical package.

RESULTS

Patient Characteristics

Overall, 263 allo-HSCT recipients developed 601 episodes of upper– and/or lower–respiratory tract symptoms and were screened for RVIs. In total, 231 allo-HSCT recipients (87%) developed at least 1 episode of a virologically-documented RVI, accounting for 458 episodes (76%) of proven RVIs. According to the algorithm selection (Figure 1), we finally included 136 allo-HSCT recipients with 161 virologically-documented RVI episodes over 5 flu seasons. Out of 136 recipients, 8 were computed twice since they changed their vaccination status during the course of the study: 2 during the same season and 6 within 2 consecutive seasons. Thus, we finally included the characteristics of 144 recipient cases according to the subjects' vaccination statuses (Table 1). There were 101 seasonally–non-vaccinated allo-HSCT recipients with 115 RVI episodes and 43 seasonally-vaccinated recipients with 46 RVI episodes who accomplished the selection criteria for comparison purposes. Of the 136 participants, 21 (15%) had computable RVI episodes in multiple flu seasons: specifically, 19 had 1 computable RVI episode in each of 2 consecutive seasons, whereas 2 recipients had 1 computable episode in each of 3 consecutive seasons.

Table 1. Patient Characteristics According to Flu Vaccine Status

Characteristics	Non-vaccinated (n = 101)	Vaccinated (n = 43)	*P* Value
Age in years, median (range)	45 (18–70)	46 (18–72)	.3
Male, n (%)	60 (60)	28 (65)	.6
Baseline disease, n (%)			
AL/MDS	64 (64)	25 (58)	.7
Lymphoid disorders	32 (32)	16 (37)	
Others	5 (5)	2 (5)	
Disease status at transplant, n (%)			.5
CR	70 (70)	34 (79)	
PR	15 (15)	4 (9)	
Refractory/active disease	16 (15)	5 (12)	
Prior ASCT, n (%)	20 (20)	10 (23)	.7
Period of transplant, n (%)			.4
2016–2017	36 (36)	13 (30)	
2014–2015	34 (34)	13 (30)	
2012–2013	22 (22)	12 (28)	
2009–2011	9 (9)	5 (12)	
Conditioning regimen, n (%)			
RIC	47 (47)	22 (51)	.7
Type of donor, n (%)			.5
HLA-identical sibling donor	31 (31)	12 (28)	
Unrelated donor	27 (27)	10 (23)	
Umbilical cord blood	26 (26)	9 (21)	
Haploidentical family donor	17 (17)	12 (28)	
Peripheral blood stem cell source, n (%	73 (73)	33 (76)	.8
HLA fully-matched, n (%)	54 (54)	20 (47)	.5
ATG as a part of the conditioning regimen, n (%)	20 (20)	10 (23)	.7
GvHD prophylaxis, n (%)			.5
Sir-Tac	15 (15)	7 (16)	
CsA + MTX	24 (24)	11 (26)	
Post-CyPh	32(32)	11 (26)	
CsA + PDN / Others	30 (30)	14 (32)	
Median time from allo-HSCT to CARV, days (range)	343 (98–4578)	592 (98–3700)	.1
Number of recipients with CARVs per seasons, n (%)			
2017–2018	33	14	
2016–2017	13	7	
2015–2016	17	6	
2014–2015	27	14	
2013–2014	11	2	
Median F-Up after CARV, days (range)	398 (30–801)	370 (100–580)	.3

There were 136 recipients included in this study. However, 8 out of these 136 recipients changed their vaccination status during the course of the study. These 8 recipients were computed twice (once in each group), according to the vaccination status at the corresponding flu season. Thus, in total we show the characteristics of 144 cases, according to vaccination status.

Abbreviations: AL, acute leukemia; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ASCT, autologous stem cell transplantation; ATG, anti-thymocytic globuline; CARV, community-acquired respiratory virus; CR, complete remission; CsA, cyclosporine A; F-up, follow-up; GvHD, graft-versus-host disease; HLA, human leucocyte antigen; MDS, myelodysplastic syndrome; MTX, methotrexate; PDN, prednisone; Post-CyPh, post-transplant cyclophosphamide; PR, partial remission; RIC, reduced intensity conditioning; Sir-Tac, sirolimus and tacrolimus.

Table 2. Clinical and Biological Characteristics of Patients at the Time of Respiratory Virus Infection Episodes According to Influenza Vaccination Status

	CARV Episodes, Non-vaccinated (n = 115)	CARV Episodes, Vaccinated (n = 46)	*P* Value
Immunodeficiency scoring index, n (%)[a]			
ANC < 0.5×10^9/L, 3pts	8 (7)	1 (2)	.3
ALC < 0.2×10^9/L, 3pts	27 (23)	7 (9)	.2
Age ≥ 40 y, 2pts	77 (67)	36 (78)	.18
Myeloablative conditioning regimen, 1pt	58 (50)	23 (50)	1
GvHD, acute or chronic, 1pt	69 (60)	17 (37)	.009
Corticosteroids, 1pt	48 (41)	10 (22)	.02
Recent or pre-engraftment allo-HSCT, 1pt	0	0	1
ISI, n (%)			
Low risk: 0–2	39 (34)	19 (41)	
Moderate risk: 3–6	65 (56)	26 (56)	.2
High risk: 7–12	11 (9)	1 (2)	
Basel immunodeficiency grading score, n (%)[a]			
Allo-HSCT ≤6 months	29 (25)	6 (13)	.1
T-cell or B-cell depletion ≤3 months	2 (2)	0	1
GvHD grade ≥2 or extensive chronic	41 (36)	9 (19)	.06
ANC < 0.5×10^9/L	8 (7)	1 (2)	.3
ALC < 0.1×10^9/L	10 (9)	1 (2)	.2
IgG < 4 g/L	34 (30)	6 (13)	.03
Basel score, n (%)			
Moderate	55 (48)	31 (67)	
Severe	38 (33)	13 (28)	.04
Very severe	22 (19)	2 (4)	
Other characteristics[a,b]			
On IS, n (%)	91 (90)	25 (54)	.003
ALC < 0.5×10^9/L, n (%)	27 (23)	8 (19)	.5
RVI characteristics and clinical consequences			
CARV LRTD, n (%)	38 (33)	8 (19)	.05
Hospital admission, n (%)	32 (27)	4 (9)	.01
Type of donor, n (%)			
HLA-identical sibling donor	36 (31)	12 (26)	
Unrelated donor	30 (26)	11 (24)	.6
Umbilical cord blood	28 (24)	10 (22)	
Haploidentical family donor	21 (18)	13 (28)	
RVI episodes/Influ RVI per seasons, n (%)			1
2017–2018	34 / 21	14 / 9	
2016–2017	14 / 6	9 / 2	
2015–2016	17 / 11	6 / 0	
2014–2015	35 / 14	15 / 3	
2013–2014	15 / 7	2 / 1	
Flu-RTD, n (%)	59 (51)	15 (32)	.036
Antiviral therapy, n (%)[c]	44 (74)	13 (86)	.5
Median time from allo-HSCT to Flu-RTD, days (range)	374 (91–4763)	724 (98–3280)	.02
Median time from allo-HSCT to flu vaccination, months (range)		16 (3–107)	
Flu-LRTD, n (%)	18 (16)	1 (2)	.01
Possible	*9 (8)*		
Proven	*9 (8)*	*1 (2)*	
Flu-related hospital admission, n (%)	16 (14)	1 (2)	.04
Overall mortality rate, n (%)	12 (23)	5 (10)	.026
Day + 30	4 (3)	1 (2)	1
Day + 60	9 (8)	1 (2)	.3
Day + 90	11 (10)	1 (2)	.1
Microbiological findings			
Respiratory virus, n			
Influ type[d]			.2

Table 2. Continued

	CARV Episodes, Non-vaccinated (n = 115)	CARV Episodes, Vaccinated (n = 46)	*P* Value
Influ-A	29	11	
Influ-B	26	4	
Influ A and B co-infection	4	0	
More than 1 RV[d]	19	5	.2
EvRh	24	15	
RSV	29	11	
HPiV	6	3	
HMPV	14	12	
CoV	5	1	
IHBoV	5	0	
ADV	3	0	

Abbreviations: ADV, adenovirus; ALC, absolute lymphocyte count; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; CARV, community-acquired respiratory virus; CoV, human coronavirus; EvRh, enterovirus/rhinovirus; Flu-RTD, influenza-related respiratory tract disease; GvHD, graft-versus-host disease; HBoV, human bocavirus; HLA, human leucocyte antigen; HMPV, human metapneumovirus; HPiV, human parainfluenza virus; HSCT, hematopoietic stem cell transplantation; IgG, immunoglobuline G; Influ, human influenza virus; IS, immunosuppressants; ISI, immunodeficiency scoring index; LRTD, lower–respiratory tract disease; RSV, respiratory syncytial virus; RV, respiratory virus; RVI, respiratory virus infection.

[a]All variables were captured at the time of BAL.

[b]The Basel immunodeficiency score was graded into moderate, severe, and very severe immunodeficiency statuses according to, respectively, the presence of 0, 1 or ≥2 of the following conditions: HSCT ≤6 months; T-cell or B-cell depletion ≤3 months; GvHD grade 2 or extensive disease; IgG < 4 g/L, neutropenia ≤0.5 × 109/L; or lymphopenia ≤0.1 × 109/L.

[c]Antiviral therapy was based on oseltamivir in all treated recipients.

[d]The numbers provided in this table only represent the viruses that were detected in cases who were selected for the comparative analyses, and do not reflect the real proportion in regards to all confirmed RVI episodes during the study period. We diagnosed 74 influenza RVI episodes, which represent 45% of the 161 RVIs. This rate means that 45% of allo-HSCT recipients with at least 1 virologically-confirmed RVI during the flu season had an episode of influenza infection. This rate does not represent the overall influenza detection in regards to all virologically-confirmed RVI episodes in that period.

Clinical and Biological Characteristics According to Vaccination Status at the Time of Respiratory Virus Infection Episodes

Patients' clinical and biological characteristics at the time of their RVI episodes are summarized in Table 2 according to their vaccination statuses. As expected, the non-vaccinated group had significantly higher rates of conditions related to poor serological influenza vaccine responses. Active GvHD, steroid therapy, ongoing immunosuppression therapy, and hypogammaglobulinemia were significantly over-represented in the non-vaccinated group as compared to the vaccinated group (60% vs 37%, 41% vs 22%, 90% vs 54%, and 30% vs 13%, respectively; $P < .05$ for all comparisons). Of note, the rate of low total lymphocyte counts at the time of RVIs at different cut-offs (<500, <200, and <100) were not statistically different among groups.

Influenza Virus Infection Characteristics

We accounted for 74 proven influenza RVI episodes over 5 flu seasons in 70 recipients, with a median time of onset of 511 days after stem cell infusion (range 98–4752). We observed a higher number of influenza RVI episodes in 2 seasons—2014–2015 (n = 19) and 2017–2018 (n = 30)—as shown in Table 2 and Figure 2. Together, these 2 seasons represent 64% of all influenza episodes over the 5 flu seasons. There were 55 episodes limited to URTD, whereas 19 (26%) involved the lower respiratory tract (9 possible and 10 proven LRTDs). The rate of hospitalization directly attributable to the influenza virus was 23% (17 out of 74 episodes). The most common influenza virus subtype was A, in 44 episodes (59%; 15 H1N1, 10 H3N2, and the remainder not subtypable), and B, in 34 episodes (46%). In 4 cases, influenza A and B were detected in the same episode/sample and were classed as co-infections.

Prevalence of Influenza Respiratory Infection and Clinical Consequences According to Vaccination Status

The observed 5-season prevalence of influenza RVIs was significantly higher in the non-vaccinated (51%) compared to the vaccinated group (36%; $P = .036$). This statistical difference was even higher regarding the influenza LRTD prevalence (16% in non-vaccinated vs 2% in the vaccinated group, $P = .01$). The progression rates of URTDs to LRTDs in recipients with influenza RVIs were 30% (18 out of 59) in the non-vaccinated group compared to 7% in the vaccinated group (1 out of 15; $P < 0.01$). Influenza-related hospital admissions were more common in the non-vaccinated group compared to the vaccinated group (14% vs 2%, $P < .05$).

Risk Factors for Influenza Infection and for Progression to Lower–respiratory Tract Disease

Logistic regression univariate and multivariate analyses of risk factors for influenza virus respiratory infections and progressions to LRTDs are shown in Table 3.

In order to identify the conditions associated with influenza virus infections, we studied the 161 evaluable recipient/episode pairs. A multivariate analysis identified the flu vaccine as the main factor associated with a reduced risk of influenza virus infection (odds ratio [OR] 0.39, 95% confidence interval [CI] 0.18–0.8, $P = .01$).

To analyze the risk factors for LRTD progression of an influenza virus infection, we focused the analysis on

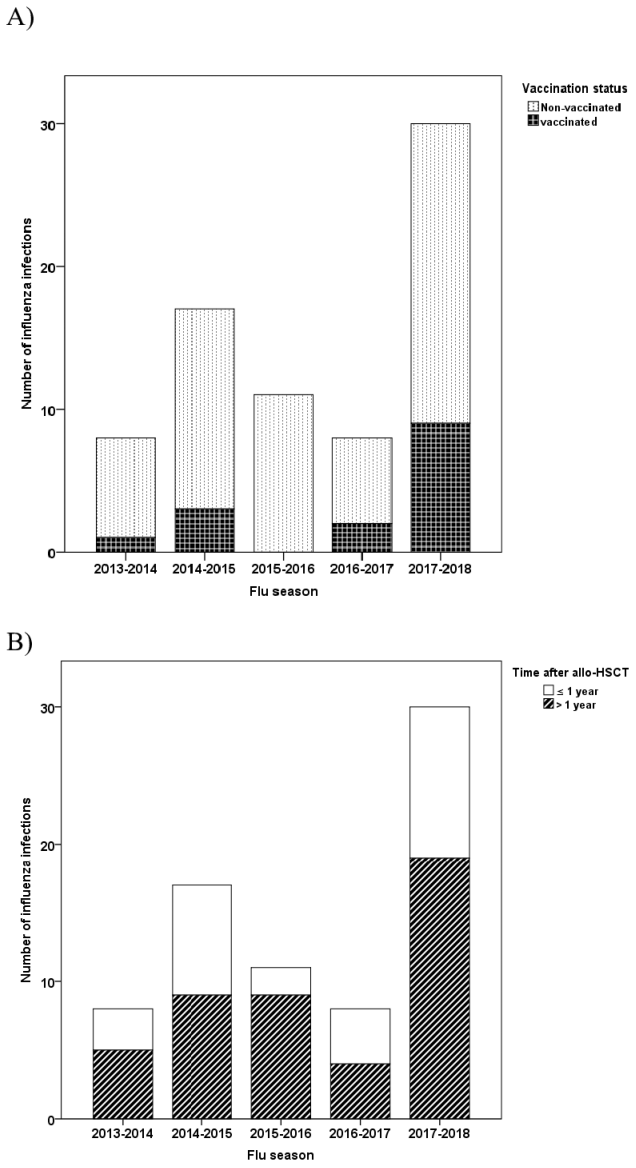

Figure 2. Number of influenza respiratory virus infection episodes according to (*A*) vaccination status and (*B*) time of infection after transplantation. Abbreviation: Allo-HSCT, allogeneic hematopoietic stem cell transplantation.

recipients/episodes with influenza virus infections (n = 74). A multivariate analysis identified 2 independent conditions associated with LRTD progression. Again, the flu vaccine was associated with a lower probability of LRTD progression (OR 0.12, 95% CI 0.014–1, P = .05). In contrast, a high-risk ISI score predicted a higher probability of the influenza virus LRTD progression (OR 36, 95% CI 2.26–575, P = .011).

DISCUSSION

This study shows that, irrespective of the flu season, a trivalent influenza inactivated vaccine given after allo-HSCT was the most important factor associated with the lower prevalence of influenza RVIs among recipients with proven CARV RVIs. In allo-HSCT recipients with influenza RVIs, a multivariate analysis showed that influenza vaccination was associated with a lower probability of the influenza virus progressing to LRTD. We also observed that a high-risk ISI score was highly predictive of influenza LRTD progression in our cohort of patients.

Although this study was not designed to assess the vaccination rate in our population, only 28% of the recipients with proven CARV RVIs received the influenza vaccine over 5 flu seasons. This agrees with prior epidemiological studies and enquiries, where the vaccination rate has ranged from 20–60% after allo-HSCT [29–31]. However, some factors merit consideration when interpreting the reported vaccination rate. We did not detect all vaccinated recipients in our prospective respiratory virus survey, since those who were vaccinated may have had lower incidences of CARV RVIs and a lower propensity to seek medical attention or testing. However, the lack of consensus across current guidelines [12–15] regarding the timing and conditions in which the influenza vaccine should be administered, in particular when immunosuppressant therapy is required to treat active/uncontrolled moderate-to-severe GvHD, is likely the most important contributor to this apparently low vaccination rate. In these scenarios, physicians may decide to defer vaccination. Thus, based on our findings, we currently recommend flu vaccination at 3 months post-transplant to all of our recipients, irrespective of their immunosuppression status.

In our selected cohort, half (51%) of the unvaccinated recipients developed influenza RVIs, with moderate to severe clinical consequences, as reflected in higher hospital admission and LRTD progression rates. To address the clinical efficacy of influenza vaccination in recipients with GvHD, corticosteroid therapy, hypogammaglobulinemia, or with ongoing immunosuppressant use, we compared the influenza RVI prevalence in vaccinated recipients according to the presence or absence of such conditions. Although the number of cases was limited, we did not find statistical differences regarding vaccinated recipients with or without GvHD (36 % vs 31%, respectively, P = .9), corticosteroids (40% vs 31%, P = .7), immunosuppressants (36% vs 29%, P = .7), or hypogammaglubulinemia (50% vs 30%, P = .1). In fact, our multivariate analysis revealed that vaccination status was the main condition associated with a lower influenza RVI prevalence in recipients with at least 1 episode of a CARV RVI. This is an important finding, since we provide clinical evidence that seasonal influenza vaccines could be clinically beneficial in allo-HSCT recipients, even when a significant number of vaccinated recipients had GvHD (19%), used immunosuppressants (54%), or used corticosteroids (22%).

Although the serological vaccination response in such recipients is poor, we can speculate that vaccination may also exert a cellular-mediated response. Influenza vaccination was able to mediate peripheral blood T-cell responses, characterized by production of the Th1 cytokine IFN-gamma by CD4+ cells,

Table 3. Univariate and Multivariate Analysis of Risk Factors for Influenza Respiratory Virus Infection and Influenza Lower–respiratory Tract Disease Progression

	Log. Regr. Influenza RTD (n = 161)				Log. Regr. Influenza Progression to LRTD (n = 74)			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
Variables	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI).	*P* Value	OR (95% CI)	*P* Value
Type of donor, n (%)								
HLA-identical sibling donor	1				1			
Unrelated donor	1.2 (0.5–2.8)	.6			0.6 (0.14–3.6)	.5		
Umbilical cord blood	0.8 (0.3–1.99)	.7			1.67 (0.41–6.7)	.4		
Haploidentical family donor	1.4 (0.6–3.5)	.4			0.5 (0.1–2.37)	.38		
ATG as a part of conditioning	1.06 (0.5–2.2)	.9			1.28 (0.38–4.2)	.7		
GvHD at the time RVI[a]	1.04 (0.5–1.9)	.8			2.24 (0.74–6.76)	.15		
On IS	1.2 (0.6–2.4)	.5			1.4 (0.4–4.9)	.59		
ALC < 0.5 × 109/L, n (%)	0.53 (0.24–1.2)	.12			3.8 (1.04–13.6)	.043	ns	
ALC < 0.2 × 109/L[a]	0.57 (0.3–1.2)	.16			3.77 (1.04–13.64)	.043	NT	
ALC < 0.1 × 109/L	0.65 (0.2–2.3)	.5			3.1 (0.41–23)	.3		
ANC < 0.5 × 109/L	0.9 (0.2–3.5)	.9			3.1 (0.4–23.8)	.2		
Age ≥ 40 years[a]	0.5 (0.28–1.09)	.09	NT		16.1 (2.01–129.4)	.009	NT	
GvHD acute >2 or Chronic Ext	0.6 (0.3–1.2)	.2			1..04 (0.31–3.4)	.9		
T- or B-cell depleted <3 months	1.17 (0.07–19)	.9			ns	1		
IgG < 4g/L	1.1 (0.5–2.3)	.8			0.8 (0.2–3.35)	.8		
Allo-HSCT ≤6 months	0.7 (0.3–1.5)	.4			1.8 (0.52–6.3)	.3		
Allo-HSCT ≤1 year					1.05 (0.3–3.1)	.9		
Myeloablative					0.93 (0.37–12.28)	.87		
Corticosteroids[a]	1.03 (0.5–1.9)	.9			3.35 (1.13–9.8)	.028	NT	
ISI								
Low risk: 0–2	1				1		1	
Moderate risk: 3–6	0.55 (0.3–1.08)	.08	ns		2 (0.6–6.6)	.25	2.3 (0.68–8)	.17
High risk: 7–12	0.6 (0.2–2.04)	.39	ns		21.6 (1.9–235.7)	.01	36 (2.26–575)	.011
Basel IG								
Moderate	1				1			
Severe	1.23 (0.6–2.4)	.5	ns		0.55 (0.17–1.8)	.3		
Very severe	0.4 (0.1–1.01)	.052	0.64 (0.4–1.02)	.057	1.2 (0.19–7.5)	.8		
Flu antiviral therapy					1.8 (0.4–7.1)	.4		
Flu vaccine	0.45 (0.2–0.9)	.033	0.39 (0.18–0.8)	.013	0.16 (0.02–1.3)	.09	0.12 (0.014–1.00)	.05

Abbreviations: ALC, absolute lymphocyte count; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ANC, absolute neutrophil count; ATG, anti-thymocytic globuline; Basel IG, Basel immunodefciency grading; CI, confidence interval; GvHD, graft-versus-host disease; HLA, human leucocyte antigen; IgG, immunoglobuline G; IS, immunosuppressants; ISI, immunodeficiency score index; Log. Regr., logistical regression model; LRTD, lower–respiratory tract disease; ns, not significant; NT, not tested; OR, odds ratio; RTD, respiratory tract disease; RVI, respiratory virus infection.

[a]These variables were not included in the final multivariate models, since they were included in the ISI score.

both in patients vaccinated more than 6 months after transplantation and those vaccinated earlier, after stem cell transpantation [10]. These data suggest that, even in cases where the expected serological response could be suboptimal (allo-HSCT <6 mo, GvHD, immunosuppressant use, or corticosteroid use), the influenza vaccine could elicit a clinical benefit through a cellularly-mediated effect, reducing the influenza infection prevalence and/or its severity.

Although the influenza RVI prevalence in vaccinated recipients was still substantial (36%), it should be noted that the risk factors for influenza LRTD progression identified vaccination as a condition associated with a reduced rate of LRTD progression. Furthermore, vaccination was also associated with a lower hospital admission rate. Given these findings, we speculate that vaccination could mitigate the severity of influenza RVIs, even in the presence of conditions related to decreased serological responses.

Another relevant finding was the usefulness of the ISI score in stratifying the LRTD progression risk of influenza RVIs, even when we analyzed episodes occurring after day 90 after stem cell infusion. ISI was developed by investigators from the MD Anderson Cancer Center to predict outcomes in allo-HSCT recipients with respiratory syncytial viruses [21]. The same investigators demonstrated its value in predicting LRTD progression in the setting of influenza RVIs [32]. Therefore, the use of the ISI could be applied to assess the need for prophylactic/therapeutic intervention with several doses of the influenza vaccine and/or with high doses of antiviral drugs in prospective studies.

Regarding influenza virus epidemiological data from the current study, most influenza RVI cases occurred in the 2014–2015 and 2017–2018 flu seasons. These data are in accordance with Spanish epidemiological data, where the influenza prevalence was significantly higher in 2014–2015 (350 cases/100 000 hab) and 2017–2018 (450 cases/100 000 hab) as compared to the 2013–2014, 2015–2016, and 2016–2017 flu seasons (270, 190, and 220 cases/100 000 hab, respectively) [33, 34]. These observations confirm that influenza RVI prevalence in our allo-HSCT recipients mimicked influenza virus prevalence in the general population.

Finally, we acknowledge that this study has some important limitations, such as the retrospective nature of the analyses, the small sample size, the somewhat heterogeneous vaccination policy, and the cohort selection method. In addition, the use of 2 different PCR methods, which differed (minimally) in their analytical performance, can be viewed as a limitation. In spite of this, our study has strengths that merit consideration. We used molecular testing. Our prospective CARV survey mirrored national epidemiological data in influenza RVIs in each flu season. We provided data encompassing 5 complete flu seasons, limiting the distortion likely introduced by the vaccination coverage variability between seasons.

In conclusion, we provide clinical evidence that influenza vaccination after allo-HSCT is associated with a lower prevalence of influenza RVI and a lower severity of the disease.

Note

Potential conflicts of interest. All authors: No reported conflicts of interest. 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.

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