

Preventive Strategies Against Cytomegalovirus and Incidence of α -Herpesvirus Infections in Solid Organ Transplant Recipients: A Nationwide Cohort Study

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We assessed the impact of antiviral preventive strategies on the incidence of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections in a nationwide cohort of transplant recipients. Risk factors for the development of HSV or VZV infection were assessed by Cox proportional hazards regression. We included 2781 patients (56% kidney, 20%

liver, 10% lung, 7.3% heart, 6.7% others). Overall, 1264 (45%) patients received antiviral prophylaxis (ganciclovir or valganciclovir, $n = 1145$; acyclovir or valacyclovir, $n = 138$). Incidence of HSV and VZV infections was 28.9 and 12.1 cases, respectively, per 1000 person-years. Incidence of HSV and VZV infections at 1 year after transplant was 4.6% (95% confidence interval [CI] 3.5–5.8) in patients receiving antiviral prophylaxis versus 12.3% (95% CI 10.7–14) in patients without prophylaxis; this was observed particularly for HSV infections (3% [95% CI 2.2–4] versus 9.8% [95% CI 8.4–11.4], respectively). A lower rate of HSV and VZV infections was also seen in donor or recipient cytomegalovirus-positive patients receiving ganciclovir or valganciclovir prophylaxis compared with a preemptive approach. Female sex (hazard ratio [HR] 1.663, $p = 0.001$), HSV seropositivity (HR 5.198, $p < 0.001$), previous episodes of rejection (HR 1.95, $p = 0.004$), and use of a preemptive approach (HR 2.841, $p = 0.017$) were significantly associated with a higher risk of HSV infection. Although HSV and VZV infections were common after transplantation, antiviral prophylaxis significantly reduced symptomatic HSV infections.

Abbreviations: av, antiviral; CI, confidence interval; CMV, cytomegalovirus; CNS, central nervous system; D, donor; HR, hazard ratio; HSV, herpes simplex virus; IQR, interquartile range; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; PCR, polymerase chain reaction; ppx, prophylaxis; R, recipient; SOT, solid organ transplant; STCS, Swiss Transplant Cohort Study; Tpx, transplant; VZV, varicella-zoster virus

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Introduction

Herpes simplex viruses type 1 and 2 (HSV-1 and HSV-2), and varicella-zoster virus (VZV) belong to the Alphaherpesvirinae subfamily and are characterized by establishing latency in the sensitive nerve root ganglia after primary infection (1,2). Both HSV and VZV infections are a common cause of mild to moderate illness in immunocompetent patients. In solid organ transplant (SOT) recipients, reactivation of HSV and VZV is common as a consequence of impaired cell-mediated immunity on

account of the immunosuppressive drugs, and the clinical manifestation tends to be more severe and prolonged than in immunocompetent individuals (3,4).

The best strategy to prevent HSV and VZV infections after transplantation has not yet been clearly defined. In the absence of antiherpes prophylaxis, up to 25–35% of seropositive patients will reactivate HSV, particularly in the first weeks following transplantation (5,6). Regarding VZV, the incidence of herpes zoster increases over months after transplantation and may affect up to 15% of patients at 5 years after transplant (7,8). Routine antiviral prophylaxis with ganciclovir or valganciclovir for the prevention of cytomegalovirus (CMV) infection has been linked to lower HSV and VZV reactivation rates (9,10). In patients who are followed by a preemptive approach (i.e. monitoring of CMV replication and administration of an antiviral drug only in patients with active replication) or have low risk of CMV infection (i.e. CMV-seronegative recipient receiving an organ from a CMV-seronegative donor [D–/R–]), specific antiherpes prophylaxis with acyclovir or valacyclovir is generally recommended to reduce the incidence of symptomatic reactivation of these viruses (4,10). However, few data have analyzed the impact of different anti-CMV preventive strategies using ganciclovir or valganciclovir on the incidence of HSV and VZV infection.

The aim of this nationwide observational cohort study was to describe the clinical characteristics and analyze the risk factors of α -herpesvirus infections after transplantation, with the particular aim of assessing the impact of the different preventive strategies (prophylaxis with ganciclovir or valganciclovir vs. a preemptive approach) against CMV infection on the incidence of symptomatic HSV and VZV infections.

Material and Methods

Study design

We conducted a nested project based on existing data from the multicenter nationwide observational Swiss Transplant Cohort Study (STCS) (11). Specifically for the current study, we included all SOT recipients enrolled in the STCS from May 2008 to December 2014. All six Swiss transplant centers participate in the STCS, and for this period, \approx 95% of all recipients of SOT performed in Switzerland consented to be included. The STCS was approved by the local ethics committee for clinical research for each participating center, and patients gave written informed consent.

Data collection

Clinical data extracted from the STCS database included demographic characteristics, type of transplant, immunosuppressive regimens (induction and maintenance drugs), pretransplant donor and recipient CMV serostatus, and pretransplant HSV and VZV serologies of the recipient. Data recorded with regard to antiviral prevention were the type of antiviral drug (ganciclovir, valganciclovir, acyclovir, valacyclovir) and the length of prophylaxis duration. Data recorded on symptomatic HSV and VZV infection were the site of infection (mucocutaneous vs.

nonmucocutaneous disease), number of episodes per patient, and use of antiviral therapy for treating active infection. From September 2012, additional data were recorded including reduction of immunosuppression and need for hospitalization following an episode of infection. We also recorded the incidence of acute rejection, graft loss, and mortality.

Clinical definitions

In the STCS, viral infections are classified according to standard definitions created by the Infectious Diseases Study Group of the STCS. Each infection episode was validated by a transplant infectious diseases specialist at each center. Symptomatic HSV or VZV disease was diagnosed when clinical manifestations were compatible with HSV or VZV infection, with or without microbiological confirmation by polymerase chain reaction (PCR). Nonmucocutaneous disease was diagnosed in case of clinical manifestations involving the gastrointestinal tract (i.e. esophagus and stomach), the eye, the respiratory tract, and the central nervous system (CNS) and/or a positive PCR in a tissue biopsy, corneal scraping, or cerebrospinal fluid, respectively. Patients with a positive PCR in blood were classified as having viremia, regardless of the presence of other clinical manifestations. Because the extension of the involvement in mucocutaneous infections was not included in the STCS database, we used need for antiviral therapy, reduction of immunosuppression, and hospitalization as surrogate markers for severity of infection.

Antiviral prophylaxis for CMV was defined as the use of ganciclovir or valganciclovir started within the first 2 weeks after transplantation. Patients without such a prophylactic treatment who were at risk of CMV disease (D+/R– and R+ patients) were considered as being managed by the preemptive approach, as described previously (12). CMV infection and disease were classified according to the definitions published by the American Society of Transplantation guidelines (13). Antiherpes prophylaxis was defined as the use of acyclovir or valacyclovir in patients not receiving anti-CMV prophylaxis. The use of universal prophylaxis or a preemptive approach for CMV and antiherpes prophylaxis was established according to each center protocol based on CMV serostatus. Because the antiviral prophylaxis (and the type of antiviral drug) depended on the CMV risk constellation, we defined four different groups: (1) CMV D–/R– patients receiving antiviral prophylaxis (either anti-CMV or antiherpes), (2) CMV D–/R– patients not receiving anti-CMV or antiherpes prophylaxis, (3) CMV D+/R– or R+ patients receiving anti-CMV prophylaxis, and (4) CMV D+/R– or R+ patients managed by the preemptive approach. Because only 19 patients in the preemptive approach group received a specific antiherpes prophylaxis, all D+/R– or R+ patients managed with a preemptive approach were analyzed as a single group, regardless of whether or not they received antiherpes prophylaxis. Acute rejection was defined for each organ following the standard international criteria (14).

Statistical analysis

A descriptive analysis was performed to determine patients' baseline characteristics (age, sex, organ transplanted, type of immunosuppressive therapy, CMV serostatus, and HSV and VZV seropositivity), transplant outcome variables (acute rejection, graft loss, death), and episodes of HSV and VZV (median number of episodes per patient, median time from transplantation, and clinical presentation). Cumulative incidence was calculated by organ group to estimate the probability of a first HSV or VZV infection event from transplant, treating death before an event as a competing risk, according to the antiviral prophylaxis used. The impact of the antiviral strategy on HSV or VZV reactivation was analyzed as a time-dependent risk factor using a Cox proportional hazards regression model, adjusting for potential confounding factors such as type of organ, episodes of rejection, age, sex, CMV preventive strategy, CMV infection,

and HSV or VZV seropositivity before transplant. The impact of the duration of antiviral prophylaxis on the probability of HSV or VZV infection was assessed by logistic regression. All analyses were performed with the statistical software R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org>).

Results

Study population

A total of 2781 SOT recipients (56% kidney, 20% liver, 10% lung, 7.3% heart, 6.7% others) were included in the study. The median age was 54 years (interquartile range [IQR] 42–62 years), and 64% were male. In addition, 76% of patients (1643 of 2155 of patients with available serology) were seropositive for HSV and 95% (2358 of 2477) were seropositive for VZV at the time of transplant. Overall, 1264 (45%) patients received antiviral prophylaxis (with ganciclovir or valganciclovir [$n = 1145$] or with acyclovir or valacyclovir [$n = 138$]) for a mean duration of 144 days (kidney, 117 days; liver, 118 days; lung, 237 days; and heart, 138 days). Baseline characteristics and outcomes of the patients according to the development of HSV, VZV, or both infections are detailed in Table 1. The calculated incidence was 28.9 cases per 1000 person-years of follow-up for HSV infection and 12.1 cases per 1000 person-years of follow-up for VZV infection.

HSV infection

The clinical characteristics of HSV infections are described in Table 2. Overall, 247 (8.9%) patients developed a total of 289 episodes of symptomatic HSV infection. Eighteen patients developed both HSV and VZV infections. The incidence of first HSV infection at 1, 3, and 6 years after transplant was 6.7% (95% CI 5.8–7.7), 8.7% (95% CI 7.6–9.8), and 9.9% (95% CI 8.7–11.2), respectively (Figure 1), with a median time of onset of 66 days after transplantation (IQR 21–336 days). The incidence by type of organ at 1 year after transplantation was 9.4% for heart, 8.4% for liver, 6.5% for kidney, and 1.8% for lung transplant recipients. Overall, 86% of HSV infections were episodes of mucocutaneous disease. Episodes of nonmucocutaneous disease included 16 infections of the gastrointestinal tract (40%), 12 episodes of keratitis (30%), six episodes of respiratory tract infection (15%), and one episode of CNS infection (2.5%).

VZV infection

In total, 110 patients (4.0%) developed VZV infections (including the 18 patients who also developed HSV infection), for a total of 121 episodes (Table 2). The incidence of VZV infection at 1, 3, and 6 years after transplant was 2.1% (95% CI 1.6–2.7), 3.5% (95% CI 2.8–4.2), and 4.4% (95% CI 3.5–5.4), respectively (Figure 1). The median time of onset was 249 days after transplantation (IQR 65–738 days). The incidence of VZV infection by

transplant type at 1 year after transplant was 2.3% for kidney, 1.6% for liver, 5.5% for heart, and 0% for lung transplant recipients. Six cases of nonmucocutaneous involvement were diagnosed, including three episodes of CNS disease, two episodes of keratitis, and one case of VZV viremia.

Impact of the antiviral preventive strategy on HSV and VZV infections

We analyzed the incidence of both HSV and VZV infections according to the CMV serostatus and the antiviral preventive strategy used after transplant (Figure 2). The incidence of HSV and VZV infections at 1 year after transplant was 4.6% (95% CI 3.5–5.8) in patients receiving antiviral prophylaxis (ganciclovir/valganciclovir or acyclovir/valacyclovir) versus 12.3% (95% CI 10.7–14) in patients without any antiviral prophylaxis ($p < 0.001$) (Figure 2A). The impact of antiviral prophylaxis was more manifest when looking specifically at HSV infection (3% [95% CI 2.2–4] versus 9.8% [95% CI 8.4–11.4] in patients with and without prophylaxis, respectively).

According to CMV serostatus, the incidence of HSV and VZV infections in D+/R– or R+ patients was 4.5% (95% CI 3.4–5.9) in patients receiving ganciclovir or valganciclovir prophylaxis and 13.2% (95% CI 11.3–15.3) in patients followed by the preemptive approach ($p < 0.001$). In D–/R– patients, the incidence of HSV and VZV infections at 1 year after transplantation was 2.5% (95% CI 0.8–5.9) versus 10.4% (95% CI 7.7–13.7) in patients with and without any antiviral prophylaxis ($p = 0.01$), respectively (Figure 2B).

When looking separately at each viral infection, the incidence of HSV infection was 2.9% (95% CI 2.1–4.1) in CMV D+/R– or R+ patients receiving ganciclovir or valganciclovir prophylaxis versus 10.6% (95% CI 8.9–12.5) in patients followed by the preemptive approach ($p < 0.001$, prophylaxis vs. preemptive) and 1.2% (95% CI 0.2–4.1) in CMV D–/R– patients receiving antiviral prophylaxis versus 8.2% (95% CI 5.8–11.1) in D–/R– patients without antiviral prophylaxis ($p = 0.01$, with vs. without prophylaxis) (Figure 2C). There were no differences in the incidence of VZV infection according to the antiviral preventive strategy used ($p = 0.53$) (Figure 2D).

Risk factors for HSV and VZV infections

Variables significantly associated with a higher risk of HSV infection in the multivariate analysis were female sex, HSV seropositivity, previous episodes of acute rejection, and use of a preemptive approach for CMV prevention in D+/R– or R+ patients compared with the reference group of D–/R– with antiviral prophylaxis (Table 3). Previous episodes of CMV infection were a significant risk factor for HSV infection in the univariate model but not in the multivariate model.

Table 1: Baseline characteristics and outcomes of patients included in the analysis according to whether they developed HSV, VZV, or both infections

Characteristics	No HSV/VZV infection n = 2442 (88%)	HSV infection n = 229 (8.2%)	VZV infection n = 92 (3.3%)	HSV and VZV infection n = 18 (0.6%)
Follow-up, years, median (IQR)	3.2 (1.6, 5.1)	4.2 (2.2, 5.8)	5 (3.1, 6.1)	4.6 (3.2, 5.8)
Sex, male, n (%)	1571 (64)	129 (56)	62 (67)	8 (44)
Age at transplant, years, median (IQR)	54 (42–62)	55 (43–61)	55 (40–62)	53 (40–64)
Transplant, n (%)				
Kidney	1352 (55)	131 (57)	56 (61)	13 (72)
Liver	491 (20)	51 (22)	15 (16)	2 (11)
Lung	270 (11)	8 (3.5)	4 (4.3)	0
Heart	166 (6.8)	19 (8.3)	14 (15)	3 (17)
Others	163 (6.7)	20 (8.7)	3 (3.3)	0
Induction, n (%)	2130 (87)	194 (85)	81 (88)	15 (83)
Basiliximab	1599 (75)	154 (79)	62 (77)	12 (80)
Rabbit anti-thymocyte globulins	596 (28)	41 (21)	20 (25)	3 (20)
Other	183 (8.6)	18 (9.3)	5 (6.1)	1 (6.7)
Maintenance immunosuppression, n (%)				
Tacrolimus	1723 (71)	150 (66)	62 (67)	10 (59)
Cyclosporine	622 (26)	70 (31)	26 (28)	7 (41)
MMF/MPA	2207 (91)	210 (93)	85 (92)	17 (100)
mTOR inhibitors	99 (4.1)	8 (3.5)	7 (7.6)	1 (5.9)
Steroids	2252 (93)	214 (94)	92 (100)	17 (100)
Other	56 (2.3)	3 (1.3)	2 (2.2)	0
HSV serology, n (%)				
Positive	1418 (58)	157 (69)	56 (61)	12 (67)
Negative	486 (20)	9 (3.9)	15 (16)	2 (7.4)
Missing	538 (22)	63 (28)	21 (23)	4 (22)
VZV serology, n (%)				
Positive	2074 (85)	185 (81)	83 (90)	16 (89)
Negative	108 (4.4)	9 (3.9)	1 (1.1)	1 (5.5)
Missing	260 (11)	35 (15)	8 (8.7)	1 (5.5)
CMV serostatus, n (%)				
D+/R–	509 (21)	23 (10)	16 (17)	2 (11)
D+/R+	812 (33)	111 (49)	33 (36)	7 (39)
D–/R+	619 (25)	53 (23)	28 (30)	5 (28)
D–/R–	502 (21)	42 (18)	15 (16)	4 (22)
CMV prevention in D+/R– or R+ patients, n (%)				
Prophylaxis	1007 (52)	41 (22)	36 (47)	1 (7.1)
Preemptive (including antiherpes prophylaxis)	933 (48)	146 (78)	41 (53)	13 (86)
Antiviral prophylaxis in D–/R– patients, n (%)				
Prophylaxis	151 (30)	5 (12)	3 (20)	1 (25)
No prophylaxis	351 (70)	37 (88)	12 (80)	3 (75)
Type of antiviral prophylaxis, n (%) (n = 1264)				
Ganciclovir	172 (15)	3 (5.8)	2 (5)	0 (0)
Valganciclovir	1003 (86)	41 (80)	35 (87)	2 (100)
Acyclovir	4 (0.34)	0 (0)	0 (0)	0 (0)
Valacyclovir	122 (9)	8 (14)	4 (10)	0 (0)
Duration of antiviral prophylaxis, days, mean (SD)	147 (202)	99 (57)	122 (80)	63 (47)
Duration of antiviral prophylaxis, n (%)				
<3 mo of prophylaxis	431 (18)	31 (13.5)	18 (20)	1 (5.6)
3–6 mo of prophylaxis	560 (23)	16 (7)	18 (20)	1 (5.6)
>6 mo of prophylaxis	180 (7.4)	4 (1.7)	4 (4.3)	0 (0)
CMV infection, n (%)	778 (32)	108 (47)	47 (51)	8 (44)
CMV infection previous to HSV/VZV infection, n (%)	—	57 (53)	30 (64)	2 (25)

(Continued)

Table 1. Continued

Characteristics	No HSV/VZV infection n = 2442 (88%)	HSV infection n = 229 (8.2%)	VZV infection n = 92 (3.3%)	HSV and VZV infection n = 18 (0.6%)
CMV disease, n (%)	164 (6.7)	30 (13)	8 (8.7)	2 (11)
CMV infection previous to HSV/VZV infection, n (%)	—	14 (47)	4 (50)	0 (0)
Acute rejection, n (%)	788 (32)	90 (40)	45 (49)	9 (50)
Graft loss, n (%)	166 (6.8)	22 (9.6)	7 (7.6)	1 (5.6)
Death, n (%)	301 (12)	29 (13)	6 (6.5)	1 (5.6)

CMV, cytomegalovirus; D, donor; HSV, herpes simplex virus; IQR, interquartile range; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; R, recipient; VZV, varicella-zoster virus.

Table 2: Clinical manifestation and management of HSV and VZV infections

	HSV infection	VZV infection
Number of patients (% of all)	247 (8.9%)	110 (4.0%)
Number of infections	289	121
Time of onset from transplantation, days, median (IQR)	66 (21–336)	249 (65–738)
Seropositivity at the time of transplant	169/180 (94%)	99/101 (98%)
Mucocutaneous disease, n (%)	249 (86%)	115 (95%)
Nonmucocutaneous disease, n (%)	40 (14%)	6 (5%)
Gastrointestinal	16 (40%)	0 (0%)
Ocular	12 (30%)	2 (33%)
Viremia	5 (13%)	1 (17%)
Central nervous system	1 (2.5%)	3 (50%)
Respiratory tract	6 (15%)	0 (0%)
Antiviral therapy, n (%)	265 (93%)	119 (98%)
Reduction of immunosuppression, n (%)	6/143 (4.2%)	3/66 (4.5%)
Hospitalization due to HSV or VZV infection, n (%)	12/143 (8.3%)	11/66 (17%)

HSV, herpes simplex virus; IQR, interquartile range; VZV, varicella-zoster virus.

Because the impact of antiviral prophylaxis on HSV infections seemed to be more important early after transplant, we built a new Cox proportional hazards model taking into consideration the period after transplant (i.e. <6 vs. >6 mo). Compared with the reference group of D–/R– with antiviral prophylaxis, the risk of HSV infection in D+/R– and R+ patients followed by the preemptive approach was only significant during the first 6 mo after transplant (hazard ratio [HR] 6.102 [95% CI 1.469–25.353], p = 0.013) compared with >6 mo after transplant (HR 1.218 [95% CI 0.417–3.383], p = 0.719). The impact of being seropositive for HSV was also higher during the first 6 mo after transplant (HR 7.582 [95% CI

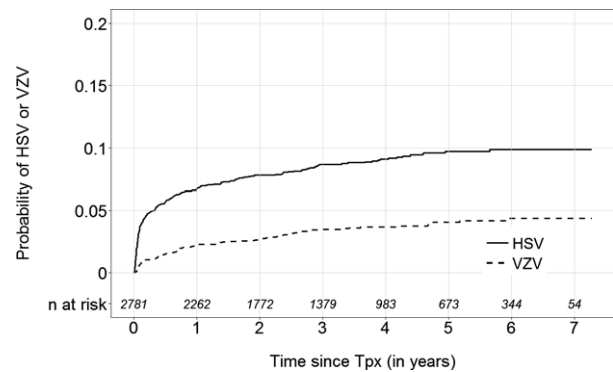


Figure 1: Cumulative incidence of HSV and VZV infections after transplantation. HSV, herpes simplex virus; Tpx, transplant; VZV, varicella-zoster virus.

3.072–18.716], p < 0.001), than later on (HR 3.102 [95% CI 1.313–7.329] p = 0.01).

For VZV infection, compared with kidney transplantation, heart transplantation was associated with a higher risk and lung transplantation with a lower risk of VZV infection, although this was not statistically significant. Age, sex, previous episodes of rejection, VZV seropositivity, and the antiviral preventive strategy were not significantly associated as risk or protective factors for VZV infection in this model (Table 4).

Of note, no particular induction or maintenance immunosuppressive regimen was associated with a higher risk of the development of HSV or VZV infections.

Impact of the duration of antiviral prophylaxis on the incidence of HSV and VZV infections

In a logistic regression, we next assessed the risk of HSV and VZV infections according whether the patients had received no antiviral prophylaxis, <3 mo, between 3 and 6 mo, or >6 mo of antiviral prophylaxis (Table 5). We found that longer duration of prophylaxis indicated lower risk of HSV infection. We did not observe any difference in the incidence of VZV according to the duration of antiviral prophylaxis.

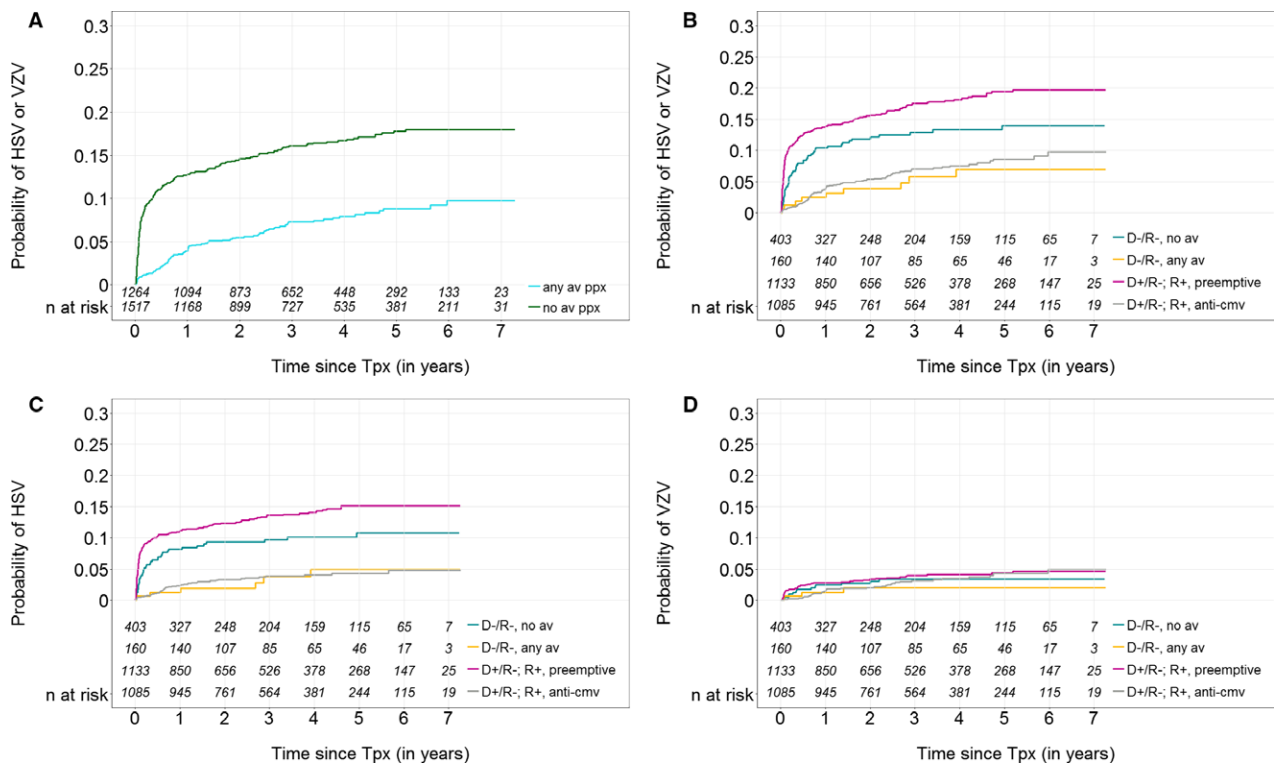


Figure 2: Probability of HSV and VZV infections after transplantation according to the CMV serostatus and the antiviral preventive strategy. Probability of HSV or VZV infection in patients with (light blue line) or without (green line) antiviral prophylaxis ($p < 0.001$, with vs. without prophylaxis) (A). Probability of infection in CMV D-/R- patients receiving antiviral prophylaxis (yellow line), CMV D+/R- or R+ patients receiving antiviral prophylaxis (grey line), CMV D-/R- patients not receiving antiviral prophylaxis (green line), and CMV D+/R- or R+ followed by the preemptive approach (magenta line): HSV or VZV infection ($p < 0.001$, all four groups) (B); HSV infection ($p < 0.001$, all four groups) (C); VZV infection ($p = 0.53$, all four groups) (D). av, antiviral; CMV, cytomegalovirus; D, donor; HSV, herpes simplex virus; ppx, prophylaxis; R, recipient; Tpx, transplant; VZV, varicella-zoster virus.

Discussion

Symptomatic HSV and VZV clinical infections were relatively frequent in the Swiss population of SOT recipients, with incidence during the first year after transplant ranging from 1.8% to 9.4% for HSV and from 0% to 5.5% for VZV, according to the type of organ transplant. These numbers are somewhat lower than those reported in other cohorts (7,8,15,16), possibly reflecting continuous improvement in the prevention and management of post-transplant viral infections in the current era of transplant medicine.

We found lower incidence of mostly HSV infections in patients receiving antiviral prophylaxis compared with patients followed by the preemptive approach or not receiving specific antiherpes prophylaxis. There are few data in the literature on the impact of antiviral preventive strategies (mostly aimed at preventing CMV infection) on α -herpesvirus infection. In a recent meta-analysis evaluating the efficacy of CMV preventive strategies in SOT recipients (17), antiviral prophylaxis and preemptive therapy showed similar efficacy in preventing HSV and VZV

infections. However, another study including 363 kidney transplant recipients analyzed the incidence of VZV reactivation according to the type of antiviral prophylaxis used. Patients were categorized into three groups: preemptive therapy, universal prophylaxis <3 mo, and universal prophylaxis >3 mo. In this setting, patients followed by preemptive therapy had higher incidence of infection compared with the other groups (80, 54.5, and 13 cases, respectively, per 1000 person-years) (18). This is in concordance with our results, in which the probability of α -herpesvirus infection was higher in patients without antiviral prophylaxis, particularly in patients followed by preemptive therapy compared with patients receiving antiviral drugs. We also observed in our study that patients receiving more than 3 or 6 mo of prophylaxis had the lowest risk of development of HSV infection. The impact of antiviral prophylaxis was seen mainly for HSV infection, likely because of the lower number of VZV infections and the fact that VZV infections appeared later on after transplantation, when most antiviral drugs were no longer prescribed as prophylaxis. This could be also explained by the presence of natural polymorphism of VZV thymidine kinase and DNA polymerase found in

Table 3: Risk factors associated with HSV infection after transplantation

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.006 (0.997–1.014)	0.188	0.999 (0.989–1.01)	0.906
Sex				
Male	Reference			
Female	1.434 (1.114–1.845)	0.005	1.663 (1.229–2.25)	0.001
HSV serostatus				
Negative	Reference			
Positive	5.082 (2.761–9.354)	<0.001	5.198 (2.787–9.693)	<0.001
Organ transplant				
Kidney	Reference			
Heart	1.422 (0.907–2.228)	0.125	1.342 (0.817–2.205)	0.245
Liver	1.09 (0.793–1.497)	0.597	0.801 (0.553–1.161)	0.242
Lung	0.321 (0.157–0.654)	0.002	0.651 (0.301–1.408)	0.275
Other	1.222 (0.765–1.951)	0.402	1.284 (0.771–2.14)	0.336
CMV preventive strategy				
D–/R– with antiviral prophylaxis	Reference			
D–/R– without antiviral prophylaxis	2.758 (1.17–6.506)	0.02	2.227 (0.894–5.549)	0.086
D+/R– or R+ anti-CMV prophylaxis	1.212 (0.519–2.828)	0.657	0.63 (0.259–1.533)	0.309
D+/R– or R+ preemptive approach	3.827 (1.691–8.661)	0.001	2.841 (1.206–6.689)	0.017
Previous CMV infection				
No	Reference		Reference	
Yes	2.567 (1.544–4.269)	<0.001	1.534 (0.808–2.91)	0.19
Induction therapy				
No	Reference			
Yes	0.803 (0.568–1.136)	0.215		
Maintenance immunosuppression				
Tacrolimus	0.794 (0.61–1.035)	0.089		
MMF	0.962 (0.726–1.274)	0.785		
mTOR inhibitors	1.246 (0.723–2.144)	0.428		
Previous episode of acute rejection				
No	Reference			
Yes	1.904 (1.278–2.839)	0.002	1.95 (1.235–3.077)	0.004

CI, confidence interval; CMV, cytomegalovirus; D, donor; HR, hazard ratio; HSV, herpes simplex virus; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; R, recipient.

in vitro studies, conferring a lower intrinsic antiviral activity of ganciclovir against VZV compared with HSV (19,20).

Our data indicate that specific antiherpes prophylaxis in patients not receiving anti-CMV drugs may further reduce the incidence of HSV and VZV infections. Of note, the antiviral agents approved for the prevention and treatment of herpesvirus infections act at the same step of virus replication, inhibiting the viral DNA polymerase. Acyclovir and ganciclovir require phosphorylation to be activated by a thymidine kinase in HSV or VZV and by its homolog UL97 protein kinase in CMV. Because acyclovir and valacyclovir are usually well tolerated and are less expensive than anti-CMV drugs, this strategy might be cost-effective in the setting of organ transplantation. This recommendation can be particularly important regarding HSV seropositivity, female gender, and therapy for acute rejection, the risk factors for HSV infection identified in our study. We found a surprising lower incidence of HSV and VZV infections in lung transplant recipients compared with other types of transplant. Although higher rates of infection have been previously

reported in lung transplant recipients (8,21–24), our results can be explained by a longer duration of antiviral prophylaxis used in these patients compared with other organ transplants. Finally, we found that both acyclovir/valacyclovir and ganciclovir/valganciclovir seemed equally effective for the prevention of α -herpesvirus infection—an expected result but not extensively reported in the literature.

Although the most common clinical presentation of α -herpesvirus infection was mucocutaneous, nonmucocutaneous involvement—feared because of its more complicated course—was detected in 10% involving infections of the gastrointestinal tract and keratitis for HSV. Of note, the data included in the STCS database did not allow us to estimate the severity of the clinical presentation, particularly regarding the rate of disseminated herpes zoster and the subsequent incidence of postherpetic neuralgia. However, we could estimate that these infections were associated with a significant burden of disease because >93% of the patients received antiviral treatment and between 8% and 17% of them required hospitalization.

Table 4: Risk factors associated with VZV infection after transplantation

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.003 (0.991–1.016)	0.604	1.004 (0.99–1.018)	0.602
Sex				
Male	Reference			
Female	0.88 (0.576–1.344)	0.555	0.958 (0.609–1.506)	0.853
VZV serostatus				
Negative	Reference			
Positive	4.75 (0.663–34.153)	0.121	4.103 (0.567–29.696)	0.162
Organ transplant				
Kidney	Reference			
Heart	2.25 (1.257–4.028)	0.006	1.783 (0.942–3.376)	0.076
Liver	0.814 (0.469–1.414)	0.466	0.713 (0.388–1.309)	0.275
Lung	0.39 (0.142–1.073)	0.068	0.428 (0.151–1.218)	0.112
Other	0.436 (0.137–1.39)	0.16	0.444 (0.139–1.422)	0.172
CMV preventive strategy				
D–/R– with antiviral prophylaxis	Reference			
D–/R– without antiviral prophylaxis	1.816 (0.517–6.372)	0.352	1.701 (0.477–6.068)	0.413
D+/R– or R+ anti-CMV prophylaxis	1.886 (0.582–6.108)	0.29	1.479 (0.452–4.844)	0.518
D+/R– or R+ preemptive approach	2.313 (0.718–7.457)	0.16	1.874 (0.565–6.221)	0.305
Previous CMV infection				
No	Reference		Reference	
Yes	1.173 (0.365–3.771)	0.789	1.082 (0.331–3.539)	0.896
Induction therapy				
No	Reference			
Yes	1.063 (0.581–1.946)	0.843		
Maintenance immunosuppression				
Tacrolimus	0.794 (0.521–1.208)	0.281		
MMF	1.292 (0.813–2.055)	0.278		
mTOR inhibitors	1.561 (0.756–3.226)	0.229		
Previous episode of acute rejection				
No	Reference			
Yes	2.423 (1.239–4.74)	0.01	1.927 (0.93–3.991)	0.078

CI, confidence interval; CMV, cytomegalovirus; D, donor; HR, hazard ratio; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; R, recipient; VZV, varicella-zoster virus.

Table 5: Logistic regression model of the probability of HSV and VZV according to the duration of antiviral prophylaxis

Duration of antiviral prophylaxis	HSV infection			VZV infection		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
<3 mo versus no prophylaxis	0.507	(0.345–0.744)	0.001	0.987	(0.575–1.693)	0.961
3–6 mo versus no prophylaxis	0.193	(0.115–0.324)	<0.001	0.803	(0.469–1.376)	0.424
>6 mo versus no prophylaxis	0.154	(0.056–0.419)	<0.001	0.567	(0.203–1.581)	0.278
3–6 versus <3 mo	0.381	(0.207–0.7)	0.002	0.814	(0.419–1.582)	0.544
>6 versus <3 mo	0.303	(0.106–0.869)	0.026	0.575	(0.192–1.721)	0.322
>6 versus 3–6 mo	0.797	(0.263–2.414)	0.688	0.706	(0.236–2.113)	0.534

CI, confidence interval; HSV, herpes simplex virus; VZV, varicella-zoster virus.

Current immunosuppressive regimens have been related with higher incidence and more severe clinical manifestations of α -herpesvirus reactivation in some studies. Mycophenolate mofetil (MMF) was identified as an independent risk factor for VZV reactivation after liver transplantation (7,21,25). Because the majority of the patients received MMF as part of the immunosuppressive

regimen, it was difficult to assess the impact of MMF on the risk of infection in our study. Gourishankar et al found that the use of induction therapy was a risk factor for VZV reactivation after transplantation (7), but this was not confirmed in the present study. In addition, we did not identify the use of mammalian target of rapamycin inhibitors, an immunosuppressive drug with antiviral properties, as a

protective factor for the development of HSV and VZV infections.

This study has several limitations. First and foremost, data on the severity and complications of the mucocutaneous involvement in VZV and HSV infection were not available in the STCS database, so we were not able to estimate the true burden of disease in view of a potential recommendation for the use of antiherpes prophylaxis in all patients not receiving anti-CMV drugs. We were not able to differentiate between HSV-1 and HSV-2 infections because of the absence of information on the localization of the mucocutaneous disease and the type of viruses involved. Moreover, we cannot exclude that some infections were underreported, particularly months or years after transplant, when patients were not exclusively followed at the transplant center. Finally, because very few D+/R– or R+ patients followed by the preemptive approach for CMV received antiherpes prophylaxis, we were not able to analyze them separately from those who did not receive any antiviral drug. Nevertheless, this is probably the largest cohort of SOT recipients with long follow-up for which the incidence and risk factors of these common viral infections have been assessed, and the results from this study may help delineate current guidelines for the management of HSV or VZV infection in the transplant population (4,26).

In conclusion, in this large nationwide cohort of SOT recipients, HSV and VZV infections were relatively common, with several cases of nonmucocutaneous involvement. Antiviral prophylaxis with ganciclovir/valganciclovir or acyclovir/valacyclovir had a significant impact on reducing the incidence of HSV infection after transplantation. Specific antiherpes prophylaxis might be recommended in patients not otherwise receiving anti-CMV drugs, especially after intensification of immunosuppression for acute rejection.

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Disclosure

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Appendix

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