GUIDELINE ARTICLE

Towards personalized prevention of Herpes zoster infection in patients with hematologic diseases or hematopoietic stem cell transplant recipients: a position paper from an *ad hoc* Italian expert panel

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Supplementary Table 1. Hematologic diseases and conditions at high risk for HZ infections for which antiviral prevention is recommended: summary of recent international guidelines

Disease or condition	AGIHO 2022 (1)	NCCN 2022 (2)
Acute myeloid leukemia	For patients with acute promyelocytic leukaemia treated with arsenic trioxide pharmacological prophylaxis during the time of treatment till 6 months thereafter is recommended to reduce VZV disease (BIIr)	
Acute lymphoid leukemia	Antiviral prophylaxis to reduce reactivation of VZV is recommended for patients with acute lymphoblastic leukaemia while on treatment (BI)	
Chronic Myeloproliferative neoplasms	Antiviral prophylaxis to reduce reactivation of VZV is recommended for patients treated with ruxolitinib while on treatment (BIIru)	Prophylaxis during ruxolitinib therapy
Non Hodgkin Lymphoma	Pharmacological prophylaxis to reduce VZV disease in non-Hodgkin lymphoma patients treated with immuno-chemotherapy is recommended (BIIu).	
Hodgkin lymphoma	There is no general recommendation for antiviral prophylaxis in patients with first line therapy of Hodgkin's lymphoma (treated with ABVD or BEACOPPesc) according to study protocols. Decision about antiviral prophylaxis has to be made on individual case basis, referring to treatment intensity and duration (CIII).	Consider prophylaxis during CD-20 targeted therapy
Chronic lymphocytic leukemia	Pharmacological prophylaxis to reduce VZV disease in CLL patients treated with (immuno-chemotherapy is recommended (BIIu). In Patients with CLL (and other Non- Hodgkin lymphoma) receiving BTK or BCL2 inhibitors antiviral prophylaxis may be recommended particularly in patients in advanced lines of therapy (CIIu). In patients receiving idelalisib high risk of infections persists for several months after therapy (BIII). The existing	Consider VZV prophylaxis in patients treated with BTK inhibitors depending on additional risk factors. Consider prophylaxis during CD-52 targeted therapy

	data about venetoclax are not sufficient to consider a specific risk for VZV reactivations and to recommend antiviral prophylaxis.	
Myeloma	Antiviral prophylaxis in patients receiving bortezomib-based treatment regimens is strongly recommend (AIIu). Prophylaxis is also recommended in patients receiving carfilzomib and ixazomib (AIIu). The existing data about IMiDs are not sufficient to consider a specific risk for VZV reactivations and to recommend antiviral prophylaxis. Prophylaxis may be considered in selected cases, taking in account the patient's individual VZV disease risk (CIIh; CIIt)	VZV prophylaxis during active therapy with proteasome inhibitors including periods of neutropenia. Consider prophylaxis during CD-38 targeted therapy.
Stem cell transplant	No specific recommendations	Consider antiviral prophylaxis for at least 6–12 months after autologous HCT. Prophylaxis should be considered for at least 1 year after allogeneic HCT.
Indications for the use of HZ vaccination	Vaccination with the adjuvated recombinant zoster vaccine (aRZV) is recommended due to safety and immunogenicity, although data on clinical efficacy in certain malignancies are preliminary and long-term protection rates are sparse.	The administration of aRZV is recommended for adult patients age ≥50 years and those ≥18 years who are at increased risk for herpes zoster disease. aRZV is recommended 50–70 days after autologous HCT. aRZV may be considered after allogeneic HCT (Efficacy in allogeneic HCT, in the presence of GVHD, or ongoing immunosuppression has not been established). The aRZV vaccine is given in 2 doses ≥2–6 months apart. For at-risk adults ≥18 years of age, a second dose can be given 1–2 months after the first dose if they will benefit from a shorter vaccination schedule. For patients who have previously received the live attenuated herpes zoster vaccine (ZVL), aRZV should be given at least 2 months after the last ZVL dose.

Supplementary Table 2. Main results of studies published since 2012 focused on the epidemiology and antiviral prophylaxis of HZ in HD and HSCT populations.

Author, year (reference)	Hematologic disease or condition (N. of pts)	Rate of HZ infection	Details on antiviral prophylaxis data
Yamakura 2014, (3)	APL (25)	HZ was documented in 7 of 15 (46.7%) pts treated with ATO but in none of 10 patients without ATO treatment. The median time of VZV reactivation was 72 days from the start of ATO	No data
Freyer 2021 (4)	APL (112)	HZ occurred in 13/112 (11.6%) pts within 6 months of completing ATO, including one case of HZ encephalitis.	HZ occurred in 17.5% of patients without versus in 4.1% of patients with AVP (RR 0.24). AVP reduced the incidence of HZ (17.5% vs. 4.1%, RR 0.24 [95% CI 0.05–1.0, p = .025]) with a number needed to treat of 7.7. HZ despite AVP occurred later than HZ in patients without AVP (7.8 vs. 2.3 months from starting ATO, p = .11). Older age and prior HZ increased the risk of HZ in patients not receiving AVP. Routine AVP should be considered in patients with APL receiving ATO, particularly in older patients and those with a history of HZ.
Glass, 2021 (5)	APL (155)	Of 102 pts treated with ATO and 53 not treated with ATO a HZ infection was documented in 14 (14%) and 1(2%) cases, respectively. The majority of these cases occurred within the first 6 months of treatment. In a multivariate analysis, ATO treatment showed a significant association with HZ infection (HR: 9.25, p = 0.04).	Of the 102 pts treated with ATO, 14 (13.7 %) received AVP at the start of therapy. Four of the 14 pts receiving AVP still developed HZ infection with a trend toward a higher proportion of herpes zoster infections among patients receiving AVP). This would suggest that prophylaxis in this cohort was used disproportionately in higher risk patients.

Barraco 2020 (6)	Myelofibrosis (426)	HZ was documented in 3.5 cases per 100 PY in 259 patients exposed to ruxolitinib versus 0.3 cases per 100/PY in 167 patients not exposed to ruxolitinib.	No data
Te Linde, 2022 (7)	Myelofibrosis and polycythemia vera (128)	Overall, 19,5% of patients treated with ruxolitinib developed HZ during treatment, in an average follow-up time of 37 months. The incidence rate was 6.9 of 100 PY being the risk to develop HZ more or less constant over the first 5 years.	No data
Cho, 2015 (8)	NHL (2188)	The overall incidence of HZ was 11.79% of the patients who received conventional chemotherapy and 12.76% of those who received rituximab-containing chemotherapy. The majority of the HZ episodes occurred within the first two years after the diagnosis of NHL.	No data
Goenaga Vázquez 2019 (9)	NHL and HL (415)	During a median follow-up of 8.9 years, the overall HZ incidence was 11.1%. Higher rates of HZ were associated with lymphocytopenia, autologous HSCT, multiple courses of chemotherapy, and fludarabine therapy. Those who received highly immunosuppressive chemotherapy had 2.9 times the risk to develop HZ than those who did not receive this therapy.	No data
Steingrímsson 2020 (10)	CLL (8989)	The incidence rate of HZ per 1000 PY in CLL pts was 2.94 compared to 0.26 in a age-/sex-/residence-matched control group.	When HZ in the calendar period 2002-2008 was compared to 1994-2001, there was a significantly decreased risk (HR 0.59). which importantly suggests that the use of AVP has resulted in decreased HZ infections despite increased risk associated with fludarabine treatment.

Coutre, 2019 (11)	CLL (330)	An integrated safety analysis of single-agent ibrutinib from randomized phase 3 studies was conducted. HZ was documented in 5% of pts treated with ibrutinib during long-term follow-up	No data
Minarik, 2012 (12)	MM (169)	There were 78 pts not receiving any AVP (46%), and 92 pts (54%) who received prophylactic ACV 200 mg/day for the whole course of bortezomib treatment and stopped with the last dose of bortezomib. Overall ,22 patients (13%) were diagnosed with HZ during bortezomib treatment, 68% of cases occurring during the first 3 cycles.	HZ occurred in only 1 patient (1%) who received AVP and in 27% of pts patients who did not. Later inspection revealed that the single patient that developed HZ despite AVP had poor adherence to the treatment, and the reactivation was caused by skipped medication. A subgroup analysis of pts with HZ history showed even higher incidence of HZ reactivation (33%).
Fukushima 2012 (13)	MM (32)	32 patients treated with bortezomib received 500 mg/day VACV prophylaxis for a median duration of 301 days. VZV reactivation developed in only one patient during AVP.	VACV at a dose of 500 mg daily appears to be effective at preventing VZV reactivation and was well-tolerated by patients with MM who received bortezomib.
Swaika 2012 (14)	MM (100)	All patients treated with bortezomib-based therapies and treated with >4 weeks of ACV prophylaxis (400 mg twice daily), which was initiated prior to starting treatment with bortezomib and discontinued 4 weeks following bortezomib, were considered.	None of the 100 MM patients receiving AVP developed HZ during treatment with bortezomib
Konig 2014 (15)	MM (93)	All pts treated with lenalidomide. VZV infection occurred in 10.7% of pts. Again, VZV infection was documented in 132 consecutive MM patients who received autologous HSCT (7.6 %) MM patients within 1 (n =5) and 2 (n =5) years after transplant.	After routine ACV prophylaxis was introduced in 2012 no further VZV infection case was documented

Leng 2018 (16)	MM (6934)	Pts treated with bortezomid or carfilzomib for ≥3 months were considered. Among them, 52.4% were dispensed zoster prophylaxis at least once.	Amongst users of AVP, 2.4% developed HZ, and amongst non-users 5.8%. In the cohort of patients who used PIs ≥6 months, both use of prophylaxis (2.6% in users versus 6.9% in nonusers) and adherence to prophylaxis (2.0% in adherent versus 4.7% in nonadherent) were independently associated with lower risk for HZ.
Lin 2023 (17)	MM (551)	AVP was given to 283 patients. Overall, 49.8% of AVP MM patients had received VACV 500 mg per day, 35.6% received ACV 200 mg per day, while the remaining 14.6% received 400 mg ACV per day. The incidence rate of HZ infection was 6.5 cases per 100 PY in the 500 mg VACV group, and 6.2 and 8.1 cases per 100 PY in the 200 mg and the 400 mg ACV groups, respectively. Pts without prophylaxis had incidence rate up to 20.6 cases per 100 PY (HR 3.28, $p < 0.001$).	The cumulative incidence of HZ infection was remarkably higher in the group who ended AVP before first-line treatment. This suggests that the use of AVP should be continued at least until the end of cancer related treatment. Non-prophylaxis group (HR: 2.37, 95% CI 1.57–3.57) had higher risk of HZ infection. The difference in dosage and types of anti-HZ drugs showed similar protective effects. In patients who stopped anti-HZ prophylaxis before active cancer-related treatment, a higher risk of getting HZ infection compared to the corresponding group was also observed (adjusted HR 3.09, $p = 0.008$).
Zheng 2022 (18)	MM (719)	The incidence of bortezomib treatment-related HZ was evaluated in pts receiving intermittent oral famciclovir prophylaxis (250mg twice daily for 9 days after finishing the last dose of bortezomib therapy every cycle) (250 pts), continuous oral ACV prophylaxis (216 pts) or no prophylaxis (253 pts).	The incidence of HZ was significantly higher in the non-prophylaxis group compared with the prophylaxis group (22.9% vs 8.2% P<0.001), while the rate was similar between the intermittent oral famciclovir group and the continuous oral acyclovir group (8.4% vs 7.9% P=0.835). Univariate analysis showed that HZ infection is strongly associated with no AVP. Other factors such as gender, age, ISS stage, type of M protein, baseline of ALC, ANC and AMC had no relationship with VZV reactivation.
Kamber 2015 (19)	Autologous HSCT (191)	Pts affected by MM. VZV reactivation occurred in 30% of patients, in 8.5% during induction and in 21.5% after HSCT, peaking at 8 months after HSCT	AVP comprised 500 mg of oral acyclovir twice daily starting on the first day after ASCT and continued for 3 weeks. As a consequence of this study internal guidelines were

			modified our and prolonged antiviral prophylaxis was recommended.
Mawatari, 2015 (20)	Autologous HSCT (97)	The cumulative incidence of VZV reactivation after a median of 1027 days after autologous HSCT was 30.7% at 1 year and 51.2% for the total observation period. The median time of the onset was 239.5 days (range 20–1798 days; IQR 126–498 days).	97% of pts received oral ACV (200 mg 5 times per day) which started at the beginning of the preparative regimen and continued until a median duration of 32 days (interquartile range 27–35 days) of HSCT. Almost all cases of HZ occurred after ACV discontinuation.
Kawamura 2015 (21)	Autologous HSCT (83)	As AVP, before August 2009, patients received oral ACV at 200 mg five times daily (ACV1000) from day 7 to engraftment, whereas after September 2009, patients received oral ACV at 200 mg once daily (ACV200). After engraftment, ACV was continued at 200 mg at the discretion of the attending physicians in both groups. Overall, 17% of pts developed VZV disease at a median of 125 days (range 38–1334) after auto-HSCT. The cumulative incidence of VZV disease after auto-HCT was 14.8 %at 1 year and 18.5 % at 2 years.	No HZ case was observed during AVP. In 62 pts who discontinued ACV before the onset of VZV disease the cumulative incidence of VZV disease after the cessation of ACV was 19.2 % at 1 year and 23.6 % at 2 years. Comparing patients who discontinued AVP at engraftment, between engraftment and 1 year after auto-HSCT, and beyond 1 year the cumulative incidence of VZV disease was 25.8 %, 7.7 %, and 0.0 % at 1 year, respectively, and 28.9 %, 17.2 % , and 0.0 % at 2 years, respectively.
Sahoo, 2017 (22)	Autologous HSCT (1000)	VZV seropositive autologous HSCT recipients with up to five years of follow up were considered. AVP with ACV 800 mg by mouth twice daily or VACV 500 mg by mouth twice daily for one year after HSCT was routinely prescribed. Post-HCT maintenance therapy protocols, especially those using steroids or bortezomib, recommended continuation of AVP for 2 months beyond completion of maintenance therapy. Over a period of five years post-autologous HSCT, 194 patients developed at least one HZ episode with a	Of the 194 patients who developed HZ 82% were not on AVP at the time of HZ. Patients taking ACV/VACV had reduced risk for HZ (adjusted hazard ratio 0.59). The median time to first HZ episode after stopping ACV/VACV prophylaxis was 4 months. Post-herpetic neuralgia was common and reported in 24% of patients with well-documented follow up.

		cumulative incidence of 21%. The incidence rate per person years over the entire follow up period was 0.06. The highest incidence rate was 0.13 in the second year.	
Zhang, 2017 (23)	Autologous HSCT, (1959)	93.0% were prescribed AVP. Average AVP duration was 220 days, while 200 (11%) patients had AVP for >1 year. HZ incidence was 42.4/1000 PY for the overall auto-HSCT cohort.	The incidence of HZ in the different AVP groups is the following: for pts who did not receive AVP HZ it was 41.3/1000 PY; for those who received AVP during the post-transplant first year HZ incidence ranged from 61.8/1000 PY for patients with AVP duration of 1–89 days to 22.6/1000 PY for patients with AVP duration of C360 days. Compared with patients who were on AVP for 1–89 days, patients with AVP duration of 180–269 days [HR = 0.576, p = 0.019], 270–359 days (HR = 0.594, p = 0.023), and >360 days (HR = 0.309, p<0.001) had significantly lower risk of HZ. Patients who did not have AVP prescriptions were probably at lower perceived risk of HZ.
Shinohara, 2019 (24)	Autologous HSCT (72)	Pts who received auto-HSCT between 2005 and 2014, without the use of AVP, were included in this study. The one-year cumulative incidence of HZ was 26.4 % (8% disseminated disease) and half of them developed post-herpetic neuralgia. A second episode of HZ occurred in 31/194 (16%) patients.	No patient received AP.
Abbasov 2022 (25)	Autologous HSCT, (107)	Pts with MM and NHL treated with autologous HSCT who received 12 months prophylactic low-dose ACV (400 mg/day) compared to 162 patients who did not receive AVP and were controlled regularly regarding HZ for at least 24 months following transplant. Overall, HZ was observed in 2.8% of patients who received AVP and in 20% in	In the group pf pts who received AVP HZ occurred after prophylaxis discontinuation, in the group who received AVP 14% and 5.6% of pts developed the viral infection during the first and second year after transplant, respectively. Neither an increase of HZ cases following AVP nor ACV refractory HZ cases were observed.

		those who did not. 30% of lymphoma pts and 14% of myeloma pts developed HZ in the first 24 months after ASCT without AVP, but only 6.3% and 0% of pts with AVP, respectively.	
Kawamura 2013 (26)	Allogeneic HSCT (141)	Pts received long term ultra low-dose ACV (200 mg/day) prophylaxis until the end of immunosuppressive therapy and for at least 1 year after HSCT. The cumulative incidence of VZV disease after HSCT was 4.5% at 1 year and 18.3% at 2 years.	Six patients experienced breakthrough VZV disease, but four of these six had not taken ACV for several weeks before breakthrough VZV disease. The cumulative incidence of VZV disease after the cessation of ACV was 28.4% at 1 year and 38.0% at 2 years.
Blennow 2014 (27)	Allogeneic HSCT (802)	VZV reactivation without routine AVP was evaluated for a median of 2.4 years. ACV prophylaxis (400 mg 2 times daily) was only used in pts who had an IgG antibody titer to herpes simplex virus of >10,000, and it was administered until engraftment. Overall, 21.4% of pts reactivated VZV at a median of 175 days after HSCT (range, 1 to 2198), resulting in a total cumulative incidence of 22.6%. There was no difference in VZV reactivation between patients receiving myeloablative conditioning or reduced intensity conditioning	No breakthrough infection during AVP could be identified.
Mascarenhas 2019 (28)	Allogeneic HSCT, (889)	All pts underwent ACV prophylaxis until 1 year after transplant or 3 months after immunosuppression discontinuation. The cumulative incidence of VZV infection was 2.8% at 1 year, and 5.8% at 2 years following HSCT	The principal finding from this study was that the use of lower dose acyclovir prophylaxis was associated with a low rate of VZV reactivation in the first year after HCT, with no evidence of clinically significant rebound at 2 years after HCT.

Baumrin 2019 (29)	Allogeneic HSCT (2163)	All patients received prophylaxis with acyclovir for at least 12 months following transplant, but 22 (1.0%) developed severe HZ at a rate of 1 per 228 person-years. Severe HZ infection occurred in a bimodal distribution during the early peri-HSCT period and at 12 to 24 months post-HSCT.	54.5% of pts were receiving ACV prophylaxis at the time of reactivation Of the 8 patients who had severe HZ at 12 to 24 months post-HSCT, 3 patients were on standard ACV dosing and concurrent immunosuppression for GVHD and the other 5 patients were not on ACV prophylaxis and were not receiving immunosuppressive medications.
Xue 2021 (30)	Cord blood transplant (227)	Cumulative incidence of HZ up to 5 years post-transplant in seropositive CBT recipients who were transplanted between 2006 and 2016 were retrospectively analyzed. Among 1-year survivors, 91% were still receiving antiviral prophylaxis, for a median duration of 20.6 months. HZ occurred in 44 patients (19%) at a median of 23.6 months. The cumulative incidence of HZ by 1 year after CBT was 1.8% (95% confidence interval [CI], .1%–4%), but increased to 26% (95% CI, 19%–33%) by 5 years.	From 2006 to 2009, institutional guidelines recommended HZ prophylaxis until immunosuppression withdrawal; after 2009, guidelines recommended HZ prophylaxis for at least 1 year and at least 8 months after immunosuppression withdrawal. Additionally, HZ prophylaxis was recommended in patients restarted on immunosuppressive therapies. In a multivariable analysis, AVP was associated with reduced risk for HZ (adjusted hazard ratio, 0.19 [95% CI, .09–.4]). in patients with a follow-up > 3 years 88% of HZ episodes occurred after AVP discontinuation.

ACV= acyclovir; AVP= antiviral prophylaxis; APL= acute promyelocytic leukemia; ATO= arsenic trioxide; CLL= chronic lymphocytic leukemia; HR=hazard ratio; HZ= Herpes zoster; MM= multiple myeloma; NHL= non Hodgkin lymphoma; Pts= patients; PY= person/years; VACV= valacyclovir; VZV= varicella zoster virus

Supplementary Table 3. Main results of real life studies on the efficacy and immunogenicity of adjuvated Recombinant Zoster Vaccine (aRZV) in hematologic malignancies (HM) and hematopoietic stem cell transplant populations (HSCT).

Author, year	Hematologic disease or condition (N. of pts)	Results of the study and comments
Muchtar, 2021 (31)	Monoclonal B-cell lymphocytosis (MBL) and CLL (37 MBL and 25 CLL pts)	The immunogenicity of aRZV was investigated and compared to historic controls matched by age and sex. An antibody and CD4+ cell response at 3 months was seen in 45% and 54% of participants, respectively, which was significantly lower compared to historic controls (63% and 96%, respectively). Lower CD4+ cell responses were observed among BTKi-treated patients compared to untreated MBL/CLL (32% vs. 73%, p = .008).
Pleyer, 2021 and 2022 (32,33)	CLL patients who were treatment naïve or receiving Bruton tyrosine kinase inhibitor therapy (106 and 96 pts evaluable for antibody and cellular response, respectively)	The antibody and cellular response rate was significantly higher in the treatment naive cohort (76.8% and 70.0%, respectively) compared with patients receiving a BTKi (40.0% and 41.3%, respectively). Antibody titers and T-cell responses were not correlated with age, absolute B- and T-cell counts, or serum immunoglobulin levels. A concordant positive humoral and cellular immune response was observed in 69.1% of subjects with a humoral response, whereas 39.0% of subjects without a humoral response attained a cellular immune response (P = .0033). Antibody titers and T-cell responses were not correlated with age, absolute B- and T-cell counts, or serum immunoglobulin levels.
Zent, 2021 and Brady 2023 (34, 35)	CLL or lymphoplasmacytic lymphoma (32 pts)	Of the 24 (75%) subjects with a humoral immune response, 21 (87.5%) also achieved a T-cell response at 4 weeks from vaccination. For the eight subjects without a humoral immune response, only four (50%) had a T-cell response. Four patients did not meet criteria for either a humoral or T-cell response. Among patients responding at 4 weeks from vaccination, 56.5% had a sustained humoral response 24 months after vaccination. The overall humoral response rate for all patients at 24 months compared to prevaccination was 41.9% . There was no significant association between prior rituximab and achieving humoral response. Cellular response was achieved in 81.3% of patients (90% CI, 66.4–91.5) 4 weeks after vaccination. Among patients who mounted T cell response at 4 weeks from vaccination, the response continued to be sustained in 65.4% of patients 24 months after vaccination. The overall cellular response rate in all patients at 24 months was 54.8%.

		This prospective study shows that patients with CLL or LPL on BTKi therapy can respond to aRZV vaccine while on BTKi therapy.
Sweiss, 2020 (36)	Multiple myeloma (85 pts)	Overall rates of seropositivity increased after 1 (87.9%; p=0.0002) and 2 (92.6%; p=0.0001) doses. Seroconversion from a baseline negative to positive test was observed in 16 (76.2%) and 23 (95.8%) patients after 1 and 2 doses, respectively
Baumrin, 2021 (37)	Allogeneic HSCT (158 pts)	In a single-center prospective observational cohort study 2 doses of aRZV were administered between 9 and 24 months after HCT, with the doses separated by >=8 weeks. There were 4 cases of HZ in the total vaccinated cohort (2.5%) and 3 cases in the modified total vaccinated cohort (28.3/1000 person-years) which was higher than that seen after RZV in healthy older adults (IR, 0.8/1000 PYs) but similar to autologous HSCT recipients (IR, 30.0/1000 PYs). All 4 HZ cases occurred during the second and third year after transplant, 10, 51, 102,115 days after the second vaccine dose and 9,10,41, 206 days after antiviral prophylaxis discontinuation. No patient was taking immunosuppressive medications at the time of HZ.
Koldehoff, 2022 (38)	Allogeneic HSCT (79 pts)	Patients received aRZV after 37 median months (range, 8–402) from transplant. Cellular immunity against various VZV antigens was analyzed by interferon-gamma ELISpot and VZV (g-E) specific immunity tested prior and post 2nd vaccination were compared. Response to VZV g-E peptide were significantly higher (from 3.2 to 5.7 fold according to measurement method) after the 2nd vaccination. Peripheral blood mononuclear cells of recipients with versus without prior shingles (n = 36 and n = 43, respectively) showed approximately twofold higher VZV-specific responses prior to and post vaccination. Immunity against glycoprotein E after the first and second vaccination, was significantly higher in males versus females. Multivariate analysis showed that shingles and sex both impacts significantly on VZV immunity. No significant correlation with the interval between transplantation and vaccination was observed. Whether the higher ELISpot responses correlate with better protection against VZV infection and reactivation needs to be clarified.

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