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Adoptive Immunotherapy for Primary Immunodeficiency Disorders with Virus-Specific T-lymphocytes

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Abstract

Background—Viral infections are a leading fatal complication for patients with primary immunodeficiency (PID) who require hematopoietic stem cell transplantation (HSCT). Use of virus-specific T-lymphocytes (VST) has been successful for treatment and prevention of viral infections after HSCT for malignant and non-malignant conditions. Here, we describe the clinical use of VST in PID at four centers.

Objective—To evaluate the safety and efficacy of VST for treatment of viral infections in patients with PID.

Methods—Patients with PID who have received VST therapy on previous or current protocols were reviewed in aggregate. Clinical information including transplantation details, viral infections, and use of antiviral and immunosuppressive pharmacotherapy were evaluated. Data regarding VST production, infusions, and adverse reactions were compared.

Results—Thirty-six patients with twelve classes of PID diagnoses received 37 VST products before or after HSCT. Twenty-six patients (72%) had been diagnosed with infections with cytomegalovirus, Epstein-Barr virus, adenovirus, BK virus, and/or human herpesvirus 6 (HHV6). Two patients were treated prior to HSCT due to EBV-associated lymphoproliferative disease (LPD). Partial or complete responses against targeted viruses occurred in 81% of patients overall. Time to response varied from two weeks to three months (median 28 days). Overall survival at six months after therapy was 80%. Four patients developed graft versus host disease (GVHD) in the 45 days following VST infusion, which in most cases was therapy-responsive.

Interpretation—VST derived from either stem cell donors or third-party donors are likely safe and effective for treatment of viral infections in patients with PID.

Keywords

Primary Immunodeficiency; immunotherapy; cytotoxic T-lymphocytes; antiviral therapy

Introduction

Primary Immunodeficiencies (PID) are a large group of congenital defects of immunity, and have many heterogeneous features, which can include abnormally frequent or severe illness from common organisms, opportunistic infections, autoimmune phenomena, and allergic disease. Among forms of PID with impaired or absent T-lymphocyte function such as severe combined immunodeficiency (SCID), viral infections are frequent and often devastating.[1,2] In children with SCID, cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and adenovirus (ADV) are the most common cases of viral-associated mortality.[3] Although antiviral pharmacotherapy exists, it is expensive, and frequently complicated by toxicities and drug resistance.[4] Response to pharmacotherapy is often incomplete without accompanying intact cellular immunity.

Definitive treatment of SCID and many other forms of PID requires reconstitution of T-cell immunity, which can be accomplished by hematopoietic stem cell transplantation (HSCT) or gene therapy for certain monogenic disorders.[5,6] Active viral infections have been shown to negatively impact survival during HSCT,[1,7] and patients with PID remain extremely vulnerable to viral infections during and after HSCT, in part due to the 3-6 months required for T cell engraftment to occur. This is of particular concern in recipients of stem cells from virus-naïve sources such as umbilical cord blood, and in patients receiving HLA-mismatched stem cell products, which require depletion of mature T-cells to prevent graft-versus host disease (GVHD).[8] Unfortunately, clearance of many viral infections is difficult or impossible without T-cell reconstitution.

Virus-specific T-lymphocytes (VST) have been used with great success in preventing and treating viral infections following HSCT.[9-11] Though methods have varied, the overall goal of VST therapy is to isolate donor T-cells with activity against one or more viruses, while excluding alloreactive T-cells that might cause GVHD. The majority of studies to date have produced VST by *ex vivo* culture and expansion of T-lymphocytes following stimulation with viral antigens using donor-derived antigen presenting cells. VST production previously required that a donor have existing immunity against the targeted viruses. However new methods using specific cytokines have permitted culture of VST from virus-naïve cord blood and adult donors, and the use of overlapping peptide pools encompassing viral antigens has reduced culture time in virus-exposed donors to 10-12 days.[12-14] VST can also be isolated directly from peripheral blood, either by selection of MHC multimer binding T-cells or by selection of T-cells that secrete interferon gamma after stimulation with viral antigens.[15,16] Selection technologies allow rapid production of VST (with under a day of processing time), but requires large volumes of blood, and can only be performed from donors that have prior viral exposure.

Most prior studies utilizing VST have focused on their administration following HSCT, and used the stem cell donor as source of VST.[9,11] Alternately, partially matched VST that have been previously generated from healthy donors and banked (third-party VST) have been used successfully as “off the shelf” therapy for viral infections or prophylaxis.[17,18] This approach eliminates the time and expense required for customized products.

Previous reports detailing the use of VST have not described their safety and efficacy exclusively in the PID setting. Thus an aggregate perspective regarding VST in PIDD is not available to physicians faced with treatment decisions. Here, we present, the largest multicenter series to date of VST use for prevention and treatment of viral diseases in the PID population.

Methods

Retrospective review was performed to collect clinical information regarding patients with PID diagnoses who received VST therapy between 2003 and 2014 at 4 institutions (Table 1). Patients received VST infusions in the context of seven clinical protocols (three closed, and four current), or off-study via compassionate use agreements. Ethical board approval was received at each institution for the administration of these novel T cell therapies (either on

existing protocols, or via dedicated emergency protocols for compassionate use), as well as for the collection of the aggregate PID data presented here.

Twenty-three of the evaluated patients were previously reported within the larger publication of their study protocol, and details were updated for this study.[20,21,23-25] The remaining patients were unpublished. Demographics, immunologic and genetic phenotype (if available), transplantation details, and the specifics of VST production and dosing were recorded, as was information on viral infections both before and after VST therapy. Antiviral responses to VST therapy were classified as complete (resolution of viremia and/or visceral symptoms), partial (≥ 1 log decrease in viral copy number and/or improvement in visceral symptoms without complete resolution, or transient resolution with subsequent return of viremia and/or symptoms within 3 months of infusion), or no response (no discernable change in viral copy number or clinical symptoms).

Results

Patient demographics

Thirty-six patients with PID received one or more infusions of VSTs during the 10-year study period (Table 2). The patients had twelve classes of underlying diagnoses (Figure 1). Severe combined immunodeficiency and X-linked lymphoproliferative disease (XLP)/ related disorders were the most common disorder types. Age at transplantation ranged from 2 months to 19 years, whereas age at VST infusion ranged from 5 months to 19 years. HSCT donors included matched related donors (4), mismatched related (haploidentical) donors (5), unrelated donors (22), and cord blood (4).

Two of the patients received VST infusions prior to planned HSCT. For those receiving HSCT, the time between HSCT and VST infusion varied from 8 days to 27 months. Twenty six patients were receiving immunosuppressive medications at the time of VST infusion, either for prophylaxis or treatment for GVHD, including calcineurin inhibitors (20), corticosteroids (16), mycophenylate mofetil (6), infliximab (1), and extracorporeal photopheresis (1). All patients receiving corticosteroids were weaned to ≤ 0.5mg/kg/day (prednisone equivalents) prior to VST infusion.

VST production and infusion

VST were produced by previously described protocols from HSCT donors, cord blood, or third-party donors.[12,23-25] Thirty-five patients received VST that were produced via culture methods (Table 1, Supplemental Figure 1), and one patient was treated with streptamer-selected VST.[15] VST were used that targeted 1 virus (19 products), 2 viruses (1 product), 3 viruses (14 products), or 5 viruses (3 products). In all cases, VST were tested for sterility, as well viral specificity by INF-γ ELISpot. Most lines (excepting some dedicated third-party VST lines[17]) were tested for lack of alloreactivity using mismatched PHA blasts or LCL as targets in cytotoxicity assays (using either ^{51}Cr release or flow cytometry-based methods[25]). Patients received VST by IV infusion at doses ranging from 5×10^6 to 1.35×10^8 cells/m^2 based on individual protocol details (Table 2).

Viral infections and response

Of the patients evaluated, 26 (72%) had been diagnosed with CMV, EBV, Adenovirus, HHV6, and/or BK virus for which they were treated. Twenty (56%) had active infection with one or more viruses, many of which were resistant to antiviral pharmacotherapy, at the time of VST infusion (Table 2). Two patients had multiple viral infections at the time of infusion. Eight patients had been diagnosed with EBV-LPD, and of these, four had ongoing EBV-LPD at the time of VST infusion. The remaining sixteen patients (44%) were treated prophylactically and had no active viral infections at the time of infusion, but were considered at high risk for infections. Of these patients, thirteen (81%) remained free of detectable CMV, EBV, and ADV following infusion, whereas the remaining three patients (19%) had reactivations of CMV or EBV, all of which resolved.

Complete or partial antiviral responses were seen in 86% of patients with CMV (n=7), 76% of patients with EBV (n=16), and all patients with ADV (n=2), and HHV6 (n=1). Six patients had reactivation of CMV (n=2) or EBV (n=4) after VST infusion. All reactivation infections resolved within 1-2 months, and in 4 patients, no antiviral pharmacotherapy was required after VST infusion. One of the two patients who were treated for multiple viral infections (Patients #16, 29) had clearance of all viruses following VST infusion. Patient #16 had clearance of EBV and HHV6 viremia, but had no improvement in BK viral load, and retrospectively the utilized VST line was shown to lack specificity against BK virus, likely due to lack of donor exposure to the virus.

Decreases in viral copy numbers in blood were seen at 2 weeks to 3 months after infusion (Figure 2), with a median response time of 1 month. There was no correlation between VST dose and likelihood of antiviral response (reduction in viral load), nor timing of response (data not shown). Antiviral efficacy was seen in most cases despite use of immunosuppressive medications including calcineurin inhibitors, MMF, and low-dose corticosteroids (<0.5mg/kg/day prednisone). In some cases, use of immunosuppressive medications during or after initial VST infusion warranted additional doses of VST. In patients #26 and #29, second VST infusions resulted in partial or complete resolution of CMV and EBV.

Of note, two patients (Patients #25 and 33) received third-party VST infusions prior to HSCT, both for EBV-LPD. Patient #33 received rituximab, cyclophosphamide, vincristine, and prednisone for treatment of EBV-LPD. She received two doses of well-matched third-party VSTs at day -21 and day -14 prior to unrelated cord blood transplantation, which was successful without further viral disease (Figure 2). Patient #25 had no response to a single dose of third-party VST for both CMV and EBV, and was found to have monomorphic EBV-associated lymphoma, which was refractory to chemotherapy.

Overall survival and adverse events following VST infusion

Overall survival in treated patients was 80% at 6 months following VST infusion. Most early deaths occurred within 3 months of therapy and were due to existing infections, including four patients who died from progressive EBV-LPD, and one patient who died due to

progressive CMV and disseminated BCG. One patient died from CNS complications of EBV-LPD at day +26 following VST infusion.

Adverse reactions following VST infusion were generally mild in all patients. Four patients (11%) developed GVHD following VST infusion, which was often associated with weaning of immunosuppression and suspected to be transplant-associated rather than attributable to VST infusion. In three of the cases, GVHD was therapy responsive without notable viral reactivation. Patient #28 developed a sterile pericardial effusion at 1 month following VST infusion, which resolved after placement of a pericardial window.

Discussion

Viral infections and reactivations are a significant cause of morbidity and mortality in patients with moderate to severe forms of PID, and account for as much as one-third of transplant-related mortality.[2,3,7] Adoptive immunotherapy with VST has been highly successful for prophylaxis and treatment of CMV, EBV, and ADV infections following HSCT in over 300 patients with both malignant and non-malignant conditions treated in Europe, Australasia and the US. Though previously limited by the costs and specialization required for production, new protocols have reduced these barriers to VST production, while widening the available donor poor for this therapy. While early diagnosis of SCID and related T-cell immunodeficiencies through newborn screening has been very successful in permitting earlier HSCT and definitive treatment prior to development of many infections,[26] the impact of viral infections on survival even after HSCT remains substantial. Further, newborn screening is not available universally and does not detect forms of PID that lack T-cell lymphocytopenia.

Here, we describe the first and largest series of patients with PID who were treated with VST for prevention or treatment of viral infections. Viral reduction or clearance was seen in the majority of patients treated, in spite of failure of antiviral pharmacotherapy in many cases. Clinical benefit was seen in spite of low VST doses, as the cells have been shown in these and other studies to be capable of expansion *in vivo* in the setting of viral infections, which has been demonstrable in prior studies by IFN-γ ELISpot analysis of the peripheral blood of patients following VST infusion.[20,27,28] Time to effect varied from 2 weeks to 3 months, with most responses seen within 1 month. Though this study was inadequately powered to evaluate the impact of cell dose on the likelihood or timing of antiviral efficacy, prior phase I trials have established that a VST dose of 2×10E7/m2 is typically well tolerated and effective.[17,28,29] Clinical benefit was seen with VST derived from a variety of donors, including HSCT donors, cord blood, and third-party donors. VST therapy was successful in a patient with CTPS1 deficiency and EBV-LPD prior to transplant (patient #33), who had clearance of disease after third-party VST therapy following which he underwent successful umbilical cord blood transplantation. One other patient has been previously reported who was similarly treated successfully in the pre-transplant period,[30] suggesting that this may be a viable bridge therapy for PID patients with refractory viral infections prior to HSCT. Recent studies of third-party derived VST following HSCT have demonstrated that even partially matched VST lines are clinically effective, as long as antiviral activity is mediated through a shared MHC allele.[17,18,31]

Most VST treatment failures occurred in patients with advanced viral disease., particularly in patients with treatment-refractory EBV LPD. Previous studies have shown that *in vivo* expansion is required for antiviral efficacy, which likely lessens the potential impact of VST in patients who are critically ill. Nonetheless, patient #31 had a rapid response to VST therapy in spite of advanced adenoviral lung disease requiring intensive care. Patient #27 failed to improve after maternal-derived VST therapy in spite of *in vitro* confirmation of antiviral restriction through shared MHC alleles. Viral escape in this case may have been due to variability within viral epitopes, graft rejection through non-shared haplotype or epitope recognition through non-shared MHC alleles.

Previous studies have demonstrated that different classes of immunosuppressive agents differentially impact T-cell proliferation and cytotoxicity. Calcineurin inhibitors have been shown to reduce proliferation but not cytoxicity *in vitro*.[32] This has been confirmed in clinical studies, as VST have been successfully used to treat EBV-LPD following solid organ transplantation in spite of the use of calcineurin inhibitors.[33] Conversely, corticosteroids do impact T-cell function, and most VST protocols to date have excluded patients on moderate to high doses of steroids.

Adverse reactions to VST infusion were generally mild, which is in agreement with most prior studies. Four cases of GVHD were described, of which three were therapy responsive and more likely due to HSCT than VST therapy. A recent review of adverse reactions to VST therapy showed that most toxicity was attributable to premedications (acetaminophen and diphenhydramine) rather than the cellular therapy itself.[34] The CNS complication in patient #34, while highly concerning, was not definitively tied to VST therapy by histology or CSF cytology.

One prior case of systemic inflammatory response syndrome was described in a cancer patient with bulky tumor burden treated with EBV-VST.[35] One report of grade III “Bystander” GVHD has been described after third-party VST therapy in a patient with adenoviremia,[36] but no similar events have occurred in many subsequent trials, including those utilizing only partially HLA matched VST.[17,18] Nonetheless, caution is prudent when considering VST therapy for patients with advanced viral disease.

This study is subject to the many limitations of retrospective analyses. Though it represents the largest collection to date of patients with PID treated with VST therapy, it remains underpowered and heterogeneous, making it difficult to draw conclusions on optimal VST dosing, or on the relative effectiveness of VST therapy versus antiviral pharmacotherapy. Additionally, studies of VST therapy have not so far utilized control groups to evaluate the impact on overall survival, though given the clear benefits of this therapy in prior trials, withholding therapy in an eligible patient would be ethically questionable.

VST represent a novel therapy for the prevention and treatment of viral infections for patients with PID before and after HSCT. Rapid advancements in production techniques promise to increase the availability of this treatment option in the coming years, while preclinical studies to target additional viruses, including RSV and influenza, may further extend the usefulness of VST therapy.[37] Given the results of this study, a phase II trial of

VST therapy for PID would be invaluable to determine whether this treatment impacts long term survival and antiviral pharmacotherapy needs. In time, both HSCT donor-derived and "off the shelf" VST therapy may become the standard of care alongside antiviral pharmacotherapy for patients with PID.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADV	adenovirus
BCG	Bacillus calmette-guerin
CMV	cytomegalovirus
EBV	Epstein-Barr virus
GVHD	graft versus host disease
HHV6	human herpesvirus 6
HSCT	hematopoietic stem cell transplantation
LCL	lymphoblastoid cell lines
LPD	lymphoproliferative disease
PBMC	peripheral blood mononuclear cells
PID	primary immunodeficiency

SCID	severe combined immunodeficiency
VST	virus-specific T-lymphocytes
XLP	X-linked lymphoproliferative disease

Clinical Implications

Therapy with VST is associated with control or prevention of targeted viruses and has minimal associated toxicity in patients with PID, and could become a standard of care in patients with viral complications before or after HSCT.

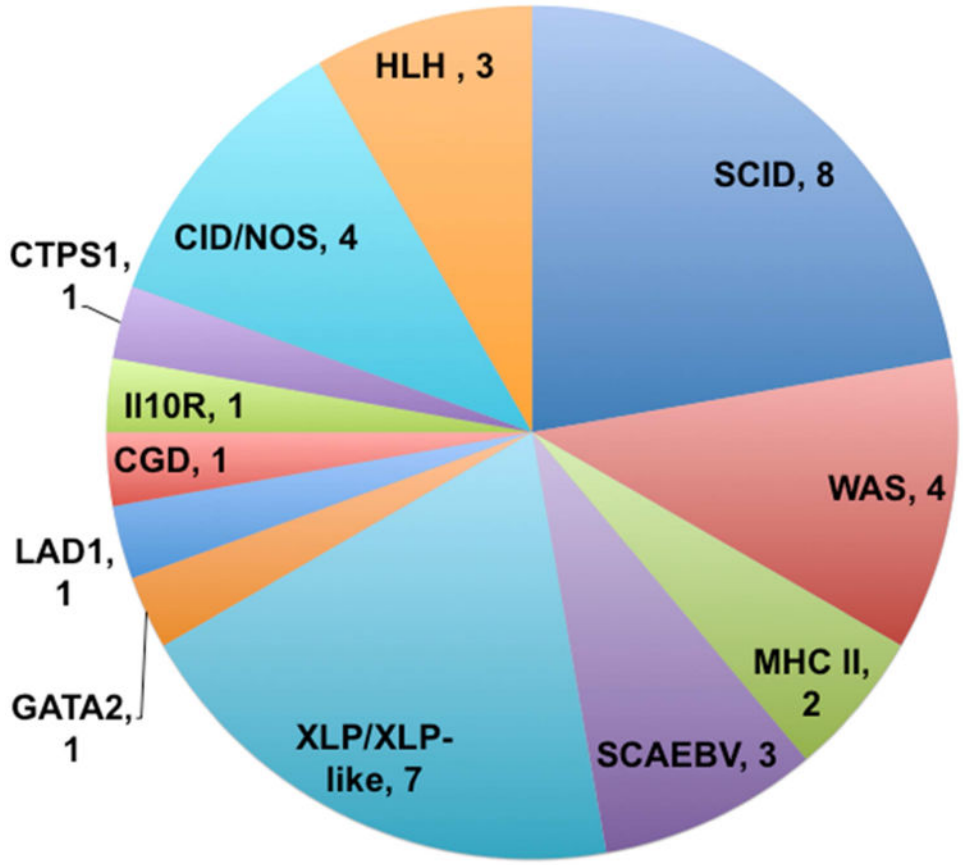

Figure 1.
Underlying forms of Primary Immunodeficiency in patients receiving VST therapy.

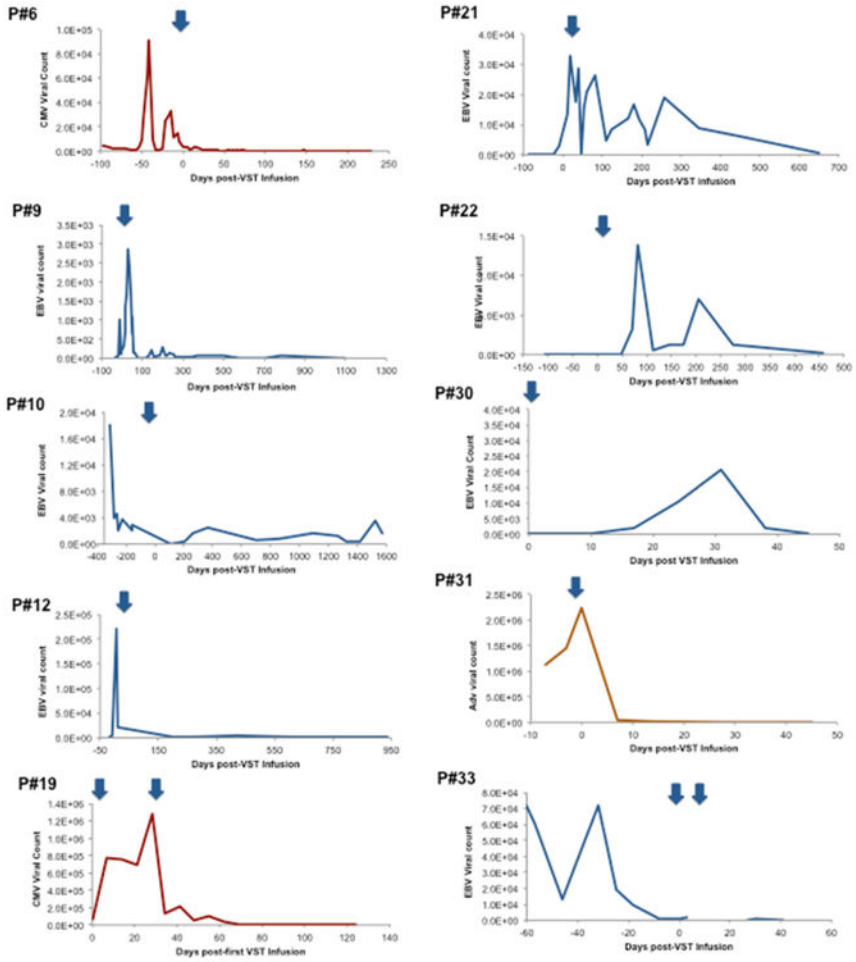

Figure 2.

Antiviral responses to VST therapy: Representative plots of Viral copy numbers (Red=CMV, Blue=EBV, Orange=ADV) over time are shown before and after VST infusion(s) (noted as blue arrows).

Table 1

VST Studies and Participating Institutions.

Study	Specificity	VST Stimulation	Manufacturing Institution	Treating Institution
ETNA NCT00058812	EBV	LCL[19]	BCM	BCM
VICTA NCT00078533	EBV/CMV/ADV	Dendritic cells and LCL transduced with Ad5/35 vector encoding pp65[20]	BCM	BCM
LYPTAIST NCT00590083	EBV/ADV	Dendritic cells and LCL transduced with Ad5/35 vector[21]	BCM	BCM
ACTCAT NCT00880789	EBV/CMV/ADV	Dendritic cells and LCL transduced with Ad5/35 vector encoding pp65[12,22]	BCM	BCM
ARMS NCT01570283	EBV/ADV/CMV/BK/H HV6	PBMC's pulsed with overlapping peptide[23]	BCM	BCM
GOS EIND	EBV	LCL	BCM	GOSH
MUSTAT (NCT01945814	EBV/CMV/ADV	PBMC's pulsed with overlapping peptide	CNMC	CNMC
TREPID	EBV/CMV/ADV	PBMC's pulsed with overlapping peptide	CNMC	CNMC
CNMC EIND	EBV/CMV/ADV	PBMC's pulsed with overlapping peptide	CNMC	CNMC
NCL EIND	EBV	LCL	Aberdeen	NCL

BCM: Baylor College of Medicine; GOSH: Great Ormond Street Hospital; CNMC: Children's National Medication Center, NCL: Newcastle Hospital; LCL: lymphoblastoid cell lines; PBMC: peripheral blood mononuclear cells.

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Table 2

Patients Characteristics and Response to VST Therapy

Center	P #	Dx	Age at HSCT	Donor	Time from HSCT to VST (mo)	Viral infections prior to VST	Viral status at time of VST infusion	Prior antiviral tmts	VST source and specificity	Immuno-suppress-ion at time of VST therapy	VST dose	Antiviral response	Adverse Events	Follow-up time (years post-HSCT)	Current status	Study # / Ref
BCM	1	IL7RA-SCID	6 mo	6/6 UCB	4.5	None	N/A	None	Cord blood, CMV/EBV/ADV	CSA, prednisone	1 dose of 1.5×10E7/m2	No detectable EBV, ADV, CMV	None	2 yrs 7 mo	Alive & well	NCT00880789 / Unpubl.
	2	IL2RG-SCID	8 mo	5/6 UCB	4.5	None	N/A	None	Cord blood, CMV/EBV/ADV	CSA/prednisone	1 dose of 2.5×10E7/m2	No detectable EBV, ADV CMV	None	2 yrs 4 mo	Alive & well	NCT00880789 / Unpubl.
	3	IL2RG-SCID	2 mo	5/6 UCB	3	None	N/A	None	Cord blood, CMV/EBV/ADV	MMF/prednisone	1 dose of 1×10E7/m2	No detectable EBV, ADV CMV	None	3 yrs 2 mo	Alive & well	NCT00880789 / Unpubl.
	4	IL2RG-SCID	2 mo	MMRD (Maternal haploidentical)	9	None	N/A	None	HSCT Donor, CMV/EBV/ADV	None	1 dose of 1×10E7/m2	No detectable EBV, ADV CMV	None	4 yr 4 mo	Alive & well	NCT00078533 / Ref 20
	5	SCID, unknown gene	1 yr	10/10 MUD	2	None	N/A	None	HSCT Donor, ADV	CSA, prednisone	1 dose of 1.35×10E8/m2	No detectable ADV	None	11 mo	Alive & well	NCT00590083 / Ref 21
	6	MHC II deficiency	10 mo	10/10 MRD	1.5	CMV	CMV viremia, pneumonitis	Foscarnet, Ganciclovir, Cytogam	HSCT Donor, CMV/EBV/ADV	CSA	1 dose of 1×10E7/m2	CMV - CR	None	2 yrs 10 mo	Alive & well	NCT00078533 / Ref 20
	7	WAS	8 mo	9/10 MMUD	5	None	N/A	None	HSCT Donor, CMV/EBV/ADV	None	1 dose of 1×10e7/m2	No detectable EBV, ADV CMV	None	5 yrs 3 mo	Alive & well	NCT00078533 / Ref 20
	8	WAS	1.2 yrs	10/10 MUD	2.3	EBV	EBV viremia	Rituximab	Donor EBV	CSA	1 dose of 2×10E7/m2	EBV – CR	None	3 yr 9 mo	Alive and well	NCT00058812 / Ref 24
	9	NK defect/ SCAEBV	12 yrs	7/10 MMUD	7	EBV	EBV viremia	Foscarnet for prior CMV	HSCT Donor, EBV	None	1 dose of 1×10E8/m2	EBV - CR	None	4 yrs	Alive & well	NCT00058812 / Ref 24
	10	SCAEBV	6.9 yrs	MRD (syngeneic)	2.5	EBV	EBV viremia	None	Donor EBV	None	1 dose of 2×10E7/m2	EBV – PR	None	4 yrs 6 mo	Died -progressive T-cell lymphoma	NCT00058812 / Ref 24
	11	SCAEBV	10.6 yrs	10/10 MUD	12	EBV-LPD	EBV resolved	Rituximab	Donor EBV	None	1 dose of 2×10E7/m2	No further EBV reactivation	None	10 yr 3 mo	Alive and well	NCT00058812 / Ref 24
	12	XLP (SLAM mutation)	19 mo	8/8 MUD	3	EBV	EBV viremia	None	HSCT Donor, EBV	CSA, prednisone	1 dose of 2×10E7/m2	EBV-CR	None	9 yrs 5 mo	Alive & well	NCT00058812 / Ref 24
	13	XLP and lymphoma	16 yrs	9/10 MMUD	2	None	N/A	None	HSCT Donor, EBV	CSA	1 dose of 2×10E7/m2	No detectable EBV	None	1 yr 6 mo	Alive & well	NCT00058812 / Ref 24
	14	LAD1	6 mo	10/10 MRD	2	ADV	ADV viremia	Cidofovir	HSCT Donor, CMV/EBV/ADV/HHV6/BK	FK	1 dose of 2×10E7/m2	ADV - CR	None	1 yr 7 mo	Alive & well	NCT01570283 / Ref 23
	15	GATA2	18 yrs	9/10 MMUD	3	BK, CMV	BK viremia	Foscarnet, ValGanciclovir	HSCT Donor, CMV/EBV/ADV/HHV6/BK	FK/prednisone	1 dose of 2×10E7/m2	BK - CR; EBV - CR *	None	1 yr 11mo	Alive & well	NCT01570283 / Ref 23
	16	HLH	19 yrs	10/10 -MUD	2	HHV6, BK	HHV6, BK viremia	None	HSCT Donor, CMV/EBV/ADV/HHV6/BK	MMF/prednisone	1 dose of 1×10E7/m2	HHV6 - CR; BK-NR, EBV-CR *	None	1 yr 10 mo	Alive & well	NCT01570283 / Ref 23
GOSH	17	CID/enterocolitis	5.9 yrs	10/10 MUD	5.3	EBV-LPD	EBV resolved	COP/Rituxima b	Donor EBV	Prednisolone	1 dose of 2.5×10E7/m2	No further EBV reactivation	None	13 years 1 month	Alive & well	EIND / Ref 24

Center	P #	Dx	Age at HSCT	Donor	Time from HSCT to VST (mo)	Viral infections prior to VST	Viral status at time of VST infusion	Prior antiviral tmts	VST source and specificity	Immuno-suppress-ion at time of VST therapy	VST dose	Antiviral response	Adverse Events	Follow-up time (years post-HSCT)	Current status	Study # / Ref
	18	CID/enterocolitis	4.7 yrs	10/10 MUD	3.7	None	N/A	None	Donor EBV	Methylpred	1 dose of 2.5×10E7/m^2	No detectable EBV	None	11 years 2 months	Alive & well	EIND / Ref 24
	19	WAS	17.7 yrs	10/10 MUD	4.3	EBV-LPD	EBV resolved	Rituximab	Donor EBV	None	1 dose of 2.5×10E7/m^2	No further EBV reactivation	None	13 years 2 months	Alive & well	EIND / Ref 24
	20	XLP	12.4 yrs	9/10 MMUD	2.4	EBV	EBV resolved	Rituximab	Donor EBV	CSA, MMF	1 dose of 2.0×10E7/m^2	No further EBV reactivation	None	10 years 6 months	Alive & well	EIND / Ref 24
	21	XLP	11.8 yrs	9/10 MMUD	3.3	EBV	EBV viremia	None	Donor EBV	CSA	1 dose of 2.0×10E7/m^2	EBV - PR	None	11 years	Alive & well	EIND / Ref 24
	22	XLP	8.7 yrs	9/10 MMUD	2.8	EBV	EBV resolved	Rituximab	Donor EBV	CSA	1 dose of 2.0×10E7/m^2	EBV - CR *	None	10 years 1 month	Alive & well	EIND / Ref 24
	23	XLP	11.8 yrs	9/10 MMUD	4	EBV-LPD	EBV viremia	COP/COP AD	Donor EBV	CSA	1 dose of 2.0×10E7/m^2	EBV - PR	None	9 years 2 months	Alive & well	EIND / Ref 24
	24	XLP-like	5.4 yrs	9/10 MMUD	2.8	EBV	EBV resolved	Rituximab	Donor EBV	CSA, Prednisolone	1 dose of 2.0×10E7/m^2	No further EBV reactivation	None	10 years 1 month	Alive & well	EIND / Ref 24
CNMC	25	ADA-SCID	N/A	N/A	Pre-transplant (6 yrs old)	EBV, CMV	EBV-LPD	Rituximab, ganciclovir	Third party (MMUD, 5/10 match), CMV/EBV/ADV	None	1 dose of 5 × 10E6/m2	EBV - NR	None	N/A	Died -EBV lymphoma, D+110	NCT025 10404 / Unpubl.
	26	SCID, unknown gene	5 mo	MMRD (Maternal 7/10)	1	CMV	CMV viremia	Ganciclovir, Foscarnet, Cidofovir	HSCT Donor (7/10 match) CMV/EBV/ADV	MMF	2 doses of 5×10E6/m2	CMV - PR	None	1 yr	Alive & well	NCT019 45814 / Unpubl.
	27	SCID, unknown gene	4 mo	MMRD (Maternal 7/12)	1	CMV	CMV viremia	Foscarnet, Cidofovir, Cytogam	HSCT Donor, CMV/EBV/ADV	None	1 dose of 1 × 10E7/m^2	CMV-NR	None	N/A	Died, refractory CMV and disseminated BCG, D+92	NCT019 45814 / Unpubl.
					2.5		CMV viremia and pneumonitis		Third-party (MMUD, 4/12 match), CMV/EBV/ADV	None	1 dose of 2 × 10E7/m2	N/A	N/A	<2 weeks		
	28	MHC II deficiency	7 mo	MRD	2	None	N/A	Acyclovir (ppx)	HSCT Donor, CMV/EBV/ADV	CSA/prednisone	1 dose of 5×10E6/m2	CMV - CR *	aGVHD grade II, pericardial effusion	10 mo	Alive & well	NCT019 45814 / Unpubl.
	29	HLH (STXBP2)	4 yrs	8/10 MMUD	1	CMV, EBV	CMV, EBV viremia	Ganciclovir, Rituximab	HSCT Donor, CMV/EBV/ADV	FK, prednisone	2 doses of 1×10E7/m2	CMV-CR, EBV-CR	Grade I cGVHD	4 mo	Alive, grade I cGVHD	NCT019 45814 / Unpubl
	30	WAS	17 months	9/10 MMUD	2	None	N/A	None	HSCT Donor, CMV/EBV/ADV	FK/prednisone	1 dose of 2 × 10E7/m2	EBV-CR *	None	2 months	Alive & well	NCT019 45814 / Unpubl.
	31	IL-10R Deficiency	10 mo	MMRD (Maternal 6/8)	0.7	CMV, ADV, HBV	ADV viremia /pneumonia	Cidofovir, Foscarnet	Third-party (Paternal, 6/8 match), CMV/EBV/ADV	None	1 dose of 2×10E7/m^2	ADV - CR, CMV-CR *	Acute GVHD, grade II gut	5 mo	Alive, ongoing GVHD	EIND / Unpubl.
NCL	32	CGD	12 yrs	11/12 MMUD	27	BK, CMV, EBV (urine) HHV6, ADV (blood), EBV-LPD	EBV-LPD	Acyclovir, rituximab	Third party (MMUD, 3/10 match), EBV	Methylpred	4 doses of 2×10E6/kg (5.9×10E7/m2)	EBV - NR	None	0.3	Died -PTLD	EIND/Ref 25
	33	CTPS1	15 mo	10/10 UCD	1 month pre-HSCT	EBV (pre-transplant LPD), RSV, ADV	EBV-LPD	Acyclovir, rituximab	Third party (MMUD, 9/10 match), EBV	None, though received COP prior to VST *	2 doses of 2×10E6/kg (3.9×10E7/m2)	EBV - CR	None	2.5 yrs	Alive & well	EIND/Ref 25
	34	HLH	7 yrs	MUD	1.7	HHV6, EBV	EBV viremia	Foscarnet, Acyclovir, rituximab	Third party (MMUD, 5/10 match), EBV	CSA/MMF/Methylpred/infliximab	3 doses of 2×10E6/kg (6.2×10E7/m2)	EBV - PR	Cerebral edema	Died 26 days after first VST dose	Died, EBV-PTLD with cerebral edema, D+76	EIND/Unpubl.

Center	P #	Dx	Age at HSCT	Donor	Time from HSCT to VST (mo)	Viral infections prior to VST	Viral status at time of VST infusion	Prior antiviral tmts	VST source and specificity	Immuno-suppress-ion at time of VST therapy	VST dose	Antiviral response	Adverse Events	Follow-up time (years post-HSCT)	Current status	Study # / Ref
	35	CID	3.7 yrs	9/10 MMUD (HLA-DQmm)	5	ADV HHV6, EBV-LPD	EBV-LPD	Acyclovir, cidofovir, rituximab, COP	Third party (MMUD, 3/10 match) EBV	Methylpred/FK/infliximab/ECP	4 doses of 2×10E6/kg (4.6×10E7/ m2)	EBV - NR	None	N/A	Died -PTLD	EIND/Unpubl.
	36	CD4 lymphopenia	13 mo	MMRD (Maternal 5/10)	8 days	Multi-drug resistant CMV	CMV-viremia	Ganciclovir, Foscarnet, Cidofovir	HSCT Donor, CMV-selected cells	CSA/MMF	1 dose of 2×10E6/kg (3.8×10E7/ m2)	CMV-PR	GVHD, grade III skin	D+280	Died of fungal pneumonia, D+280	EIND/Unpubl.

Abbreviations: P#: Patient #; TMTS: treatments; BCM: Baylor College of Medicine; CNMC: Children's National Medical Center; NCL: Newcastle Hospital; GOSH: Great Ormond Street Hospital; UCB: Umbilical cord blood, MMRD: Mismatched related donor; MRD: matched related donor; MMUD: mismatched unrelated donor; MUD: matched unrelated donor; ADV: adenovirus; LPD: lymphoproliferative disease; COP: cyclophosphamide/ vincristine/ prednisone; COPAD: cyclophosphamide/vincristine/ prednisolone/doxorubicin; CSA: Cyclosporin A; MMF: Mycophenylate mofetil; FK: Tacrolimus; CR: complete response; PR: partial response; NR: no response; BCG: Bacillus-calmette-guerin; PTLD: post-transplantation lymphoproliferative disease; Mo: months; Yrs: years.

*Asterisks denote viral infections/reactivations that occurred following VST infusion. Follow-up time () is as of 12/31/2014. Rows corresponding to patients who were prophylactically treated with VST are shown in grey.