Published in final edited form as:

J Allergy Clin Immunol Pract. 2019 March ; 7(3): 809–818. doi:10.1016/j.jaip.2018.10.049.

Virus-specific T-cells: Current and Future Use in Primary Immunodeficiency Disorders

Katherine M. Harris, MD¹, Blachy J. Davila, MD^{1,2}, Catherine M. Bollard, MD^{1,2}, and Michael D. Keller, MD^{1,3}

¹Center for Cancer and Immunology Research, Children's National Health System, Washington, DC

²Division of Blood and Marrow Transplantation, Children's National Health System, Washington, DC

³Division of Allergy & Immunology, Children's National Health System, Washington, DC

Abstract

Viral infections are common and can be potentially fatal in patients with primary immunodeficiency disorders (PIDD). Since viral susceptibility stems from poor to absent T cell function in most patients with moderate to severe forms of PIDD, adoptive immunotherapy with virus-specific T-cells (VST) has been used as to combat viral infections in the setting of hematopoietic stem cell transplantation in multiple clinical trials. Most trials to date have targeted cytomegalovirus, Epstein-Barr virus, and adenovirus either alone or in combination, though newer trials have expanded the number of targeted pathogens. Use of banked VSTs produced from third-party donors has also been studied as a method of expanding access to this therapy. Here we review the clinical experience with VST therapy for patients with PIDD as well as future potential targets and approaches for use of VSTs to improve clinical outcomes for this specific patient population.

Keywords

T cell; immunotherapy; primary immunodeficiency

INTRODUCTION

Primary Immunodeficiency Disorders (PIDD) are a growing spectrum of defects in adaptive and innate immunity, ranging from potentially fatal diseases of infancy to subtle abnormalities with onset in later life.(1) Severe combined immunodeficiency (SCID) and

Corresponding author: Michael D Keller, Children's National Health System, 111 Michigan Ave NW, 6th floor SZL, M7729, Washington, DC 20010, mkeller@childrensnational.org, Phone: 202-476-5843, Fax :202-849-4831.

Conflicts of Interests Disclosures: KMH, BJD, and MDK have no financial conflicts of interest to disclose. CMB serves on the scientific advisory boards of Neximmune, Torque and Collectis and is a co-Founder of Mana Therapeutics.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

other major forms of PIDD are targets for early identification in order to allow definitive therapy such as hematopoietic stem cell transplantation (HSCT) or gene therapy prior to onset of potentially life-threatening infections.(2, 3) In this regard, newborn screening via the TREC assay has been highly successful in enabling early identification and preventative care for this population.(4) Beyond SCID, the diagnosis of many other profound forms of PIDD are an indication for hematopoietic stem cell transplantation.(5, 6) Many studies have demonstrated that the presence of active infections in recipients undergoing transplantation adversely impacts survival.(2, 3, 7) Viral infections are very common in patients with forms of PIDD impacting adaptive immunity, and in spite of the success of antiviral medications, respiratory viruses and herpesviruses remain leading contributors to transplant-associated mortality.(5, 8, 9)

For over 20 years, adoptive immunotherapy with virus-specific T-cells (VSTs) has been utilized predominantly in the setting of HSCT for patients with malignancies.(10–24) Early studies predominantly focused on treatment of cytomegalovirus and Epstein Barr Virus by infusing T-cells derived from stem cell donors recognizing viral epitopes shortly after HSCT, and therefore narrow the time window during which recipients have absent effector T-cell function. VST production methods have been recently reviewed.(25) Briefly, early methods utilized EBV-transformed lymphoblastoid cell lines derived from the donor to generate T-cell products after repeated culture stimulations over several weeks.(17, 19) Advances in VST generation utilized viral transduction or transfection of antigen presenting cells in order to generate VST products recognizing multiple viruses (Figure 1).(16) Most recently, use of peptide libraries spanning multiple viral antigens has allowed rapid expansion of VST products targeting a wide range of viral targets in 10–12 days.(26) Other methods for generating VSTs using rapid selection technologies have also been successful using either MHC multimers for a given viral epitope, or using cytokine capture technologies with immunomagnetic bead separation.(27–31) These methods have the advantage of rapid VST production (i.e. within 24 hours), as well as the use of a commercially available closed system.

Over the past two decades, more than 500 patients have received VSTs in various phase I-II trials internationally. Though most VST use has been in the setting of HSCT for malignant conditions, a proportion of patients with PIDD have been included in these published trials. Most VST products have been derived from stem cell donors for use post-HSCT, but several studies have demonstrated the utility of administering partially HLA-matched VSTs derived from healthy third-party donors as an “off the shelf” VST therapy.(24, 32–37) Successful antiviral responses following third-party VST therapy has improved over time as methods of donor/recipient matching has improved, with response rates in recent trials ranging from 75–92%. (36–38)

Monoviral VSTs in PIDD

EBV, CMV, and adenovirus are among the most common viral causes of morbidity and mortality in patients with PIDD receiving HSCT, and have been the targets of most monoviral VST trials (Table 1). Many early studies utilized *ex vivo* expansion to produce monoviral VST products. A large study by Heslop *et al* treated 114 patients with donor-

derived EBV-specific VSTs post HSCT. Within this trial, 14 patients received their HSCT for an underlying PIDD.¹⁴ The majority of the patients in this study were treated prophylactically since a history of an EBV-related malignancy or underlying primary immunodeficiency placed them at high risk for developing EBV-lymphoproliferative disease (EBV-LPD) in the T-cell depleted transplant setting. The remaining patients were treated for active EBV-LPD or lymphoproliferation. Of the PIDD patients with active EBV reactivation at the time of infusion, 3 of 6 had complete virologic response to the EBV-specific T cell therapy. Three patients had partial virologic responses, of whom two are alive and one patient died of progression of T-cell lymphoma. Eight patients with PIDD received the EBV T cells as adjuvant therapy post HSCT including six patients with a history of viremia or EBV-LPD. None of these patients developed EBV reactivation post-infusion.

In the CMV setting, Bao *et al.* administered CMV-specific VSTs generated using peptide expansion to treat 7 patients who had refractory CMV post HSCT. Three of these patients had underlying PIDD diagnoses and of these patients, 2 of the had a complete virologic response.³⁸ The non-responding patient had recurrence of viremia in the setting of corticosteroid use for relapsing hemophagocytic lymphohistiocytosis (HLH), and eventually died of fungal pneumonia.

Several phase 1 trials have evaluated immunomagnetic selection to generate VSTs to prevent and treat serious viral infections in transplant patients with both malignant and non-malignant diseases, including primary immunodeficiency disorders. Feuchtinger *et al.* generated adenovirus specific VSTs which were administered to 9 patients (one with PIDD), for adenoviremia refractory to multiple drugs post HSCT.⁽³⁰⁾ Five of six evaluable patients had complete responses, including resolution of adenoviral infection in the patient with PIDD. A follow-up study by the same group treated 30 patients for adenoviremia, of whom 7 patients had immunodeficiency. They achieved clearance of adenovirus in 14 and partial responses in 7 patients, though further breakdown by diagnosis was not provided.⁽²⁷⁾ The difference in adenovirus related mortality in VST responders versus non-responders was significant- 9.5% versus 100%, respectively. In a recent French multi-institutional study led by Necker Hospital for Sick Children, Creidy *et al.* treated 15 patients with CMV, adenovirus, or both viruses with VSTs targeting a specific virus.⁽³¹⁾ Of these patients, 5 had PIDDs. Three of the PIDD patients were treated with CMV-specific VSTs, 1 with adenovirus (Adv)-specific VSTs, and one patient received both CMV and Adv-specific VSTs. Three of these patients had virologic responses (2 to CMV and 1 to Adv) and were alive at follow-up. Two of these patients had stabilization of viral retinitis, while one had vision loss (Table 1). The two non-responding patients died of pulmonary disease (one following treatment of CMV, and one following treatment of Adv).

Multiviral VSTs in PIDD

The majority of VST studies over the past decade have administered VST products specific for multiple viruses using different *ex vivo* expansion manufacturing approaches.^{15,16,21} Leen *et al* from Baylor College of Medicine treated a patient with SCID with trivirus specific T-cells generated using EBV-transformed B cells transduced with an Ad5f35CMVpp65 vector to stimulate and expand EBV/CMV/Adv specific T cells. The

patient with SCID received these VSTs for Adv infection and achieved a complete response. (16) In a follow-up study by the same group, donor-derived VSTs with specificity to EBV and Adv were given to patients following HSCT. In this study, one patient with SCID was treated prophylactically. Expansion and persistence of EBV-specific T-cells was observed in the peripheral blood of this patient post infusion, corresponding with a lack of viral reactivations or infections. (15) Subsequently, this group produced VSTs targeting EBV, CMV, and Adv antigens utilizing a rapid expansion methodology where antigen presenting cells nucleofected with plasmids encoding viral antigens (Hexon/Penton for Adv, IE1/pp65 for CMV and LMP2/BZLF1 for EBV) were used to stimulate and expand multivirus specific T cells.¹³ These tri-specific VSTs were used to treat 10 patients, including 1 patient with HLH who had dual infection with CMV and adenovirus. This patient achieved a complete response against both viruses.⁶ In a recent retrospective study pulling together the combined VST experience at Baylor College of Medicine, Children's National, Newcastle University, and the University of Aberdeen, Naik *et al.* described 13 previously unpublished patients with PIDD who received donor-derived VSTs after HSCT. (39) Eight of these patients were treated prophylactically and had no viral infections or reactivations post VSTs. Five patients were treated for CMV or EBV with complete viral clearance achieved in four patients post VSTs. The group at Baylor College of Medicine (Papadopoulou *et al.*) subsequently used APC pulsed with overlapping peptide pools specific for 12 different viral antigens to generate VSTs with activity against 5 viruses: EBV, CMV, adenovirus, BK virus, and HHV6.¹² Eleven patients were treated on this study, including 4 with PIDD who received VSTs as treatment for up to 3 concurrent viral infections. At 12 weeks post-infusion, 3 of the 4 PIDD patients achieved a complete virologic response. The fourth patient achieved a complete response to EBV and HHV6, but no response to BK virus which was related to the fact that the VST product infused did not have specificity for BK virus (Table 1).

Third-party derived VSTs in PIDD

Though donor-derived VSTs have been very successful in prior trials, use of third-party VSTs from specialty T-cell banks eliminates the time period required for production and the need for an available donor, and has the potential to vastly widen availability of this therapy. There is limited data on third-party VSTs specifically for patients with PIDD. However, several studies to date have evaluated use of third-party VSTs in patients with a variety of diagnoses that have demonstrated efficacy in the setting of treatment-refractory viral disease (Table 1). The group at the University of Aberdeen (Vickers *et al.*) described 3 patients with PIDD who were treated for EBV-LPD with third party EBV-specific T cells, one of whom achieved a complete response. (33) The group at MSKCC (Doubrovina *et al.*) similarly described one patient with X- linked lymphoproliferative syndrome who received third party EBV-specific VSTs for EBV-LPD post HSCT, achieving a complete remission. (24) In the multicenter retrospective analysis by Naik *et al.*, 4 previously unpublished patients with PIDD received third-party VST for post-HSCT viral infections. One of these patients cleared both adenovirus and CMV. Two patients died of progressive EBV-LPD, and another had a partial response to CMV, but later died of fungal pneumonia. The group from Westmead Institute and the University of Sydney (Withers *et al.*) similarly studied the use of partially HLA-matched "off the shelf" VSTs in 30 patients. (38) Three of these patients had PIDD; 2

were treated for adenovirus, and one patient was treated for EBV. All three patients achieved a complete response and were alive 12 months post-infusion (Table 1).

Though the majority of VSTs have been administered to patients post HSCT, viral infections are also a serious complication prior to HSCT in patients with SCID and other profound forms of PID. Several case reports have described the use of VST in this setting. Wynn *et al.* from the University of Edinburgh used third party EBV-specific VSTs for the treatment of a patient (who was later shown to have CTPS1 deficiency(39)) with primary CNS, EBV-associated lymphoma who had a poor initial response to chemotherapy.(40) The patient received 2 VST infusions resulting in a significant clinical improvement and undetectable levels of EBV viremia, allowing the patient to proceed to HSCT. The patient did have EBV reactivation post HSCT, but again achieved a complete response with rituximab and two additional third-party VST infusions. Uhlin *et al.* at Karolinska University described the use of maternally-derived VSTs targeting a dominant HLA-A02:01-restricted epitope on CMV-pp65 (NLVPVATM) to treat an infant with SCID and drug-refractory CMV infection.(41) A partial virologic response was seen with 10-fold decrease in viral load, but the infant died after subsequent umbilical cord blood transplantation. Miller *et al.* described the use of third party adeno-specific VSTs manufactured at Children's National for a patient with RAG1 SCID and disseminated adenoviremia treated under eIND at Phoenix Children's Hospital. (42) Prior to transplant, the patient received two doses of third party VSTs that were 3/10 HLA matched with the patient, followed shortly thereafter by HSCT from a matched unrelated donor. Nineteen days after the second VST infusion (11 days post HSCT), the patient had undetectable levels of adenovirus.

Safety of VSTs in PID

Many previous phase I studies and case reports have shown VSTs to be safe. In the current literature, infusion reactions are rarely described, and were always mild when reported.(43) It is likely these mild reactions are likely secondary to preservatives used during cryopreservation (e.g. DMSO) or the concomitant use of benadryl, rather than the T cells per se. While most phase I studies do describe a number of adverse events, they are usually not attributable to the infusion, and are likely a reflection of the high morbidity population that is usually in need of infusions. The main concern with T cell infusions is potential alloreactivity of the product however, multiple reports suggest that GVHD and CRS rates are very low.(10, 44)

Graft versus host disease (GvHD)—The most commonly discussed potential risk following T-cell infusion is the development of graft versus host disease post VST infusion. As previously described(44), current methods of VST manufacture decrease the overall risk of GvHD by infusing mostly, if not all, effector cells, therefore reducing alloreactive cells in the final product. In a multicenter study, Leen *et al.* reported that of the 50 patients treated with third-party VST, 8 (16%) developed GvHD post T cell infusion.(37) GvHD was low grade in 7/8 patients (stage I in 6, stage II in 1) with one grade III liver GVHD developing in a patient with disseminated adenovirus disease. Most (75%) of the patients who reported GVHD post VSTs had a history of GvHD prior to T cell infusion. Most published studies report a similarly low incidence of graft versus host disease in the donor-specific and third

party VST settings.(21, 23, 24) When GVHD has developed post T cell infusion, it is typically low grade and tends to easily resolve with therapy.(39) Interestingly, the incidence of GvHD is not appreciably different between studies when donor-derived versus third-party derived VST products are administered.(45) It is important to note, however, that current data is predominantly available from phase I and retrospective studies which lack control groups. Therefore, it remains yet to be proven if this rate is in fact different from what would be expected in the general post HSCT population.

Cytokine Release Syndrome (CRS)—CRS is a form of systemic inflammatory response syndrome, caused by a large, rapid release of cytokines into the blood from immune cells.(46) When severe, it can present with high fevers, hypotension, and multi-organ dysfunction. Given the high rates of cytokine release syndrome seen with chimeric-antigen receptor (CAR) therapy, it stands to reason this could be a potential risk of VSTs. (47) To date, cases of CRS have been very rare after VST infusion, though it has been described, particularly in cases with high viral burden.(48) There are 2 reports of worsening respiratory and hepatic status post VSTs, both in the setting of severe adenoviremia.(31, 49) These were considered potentially attributable to the T cell infusion, though these are also well described virus-associated complications in the immunocompromised host. There are also two reports of respiratory failure after EBV-specific T cell infusions, both in the context of an inflammatory reaction to bulky EBV disease in the upper chest.(14) It is therefore advisable to monitor for CRS post infusion, particularly in cases with high viral loads or bulky disease.

Graft Rejection/Allosensitization—Potential allosensitization against HLA proteins is a big concern in the bone marrow transplant population. Graft rejection is a particular concern with use of third party VSTs that may be partially mismatched with the stem cell donor, but this has not been seen in the many trials reporting the use of third-party VSTs in this setting. Allosensitization is also a theoretical concern when administering third party VSTs for patients with PIDD prior to HSCT, but considering the underlying immunodeficiency present in patients with forms of PIDD that warrant transplantation, this theoretical risk is thought to be low. Miller *et al.* described secondary graft loss in a patient with RAG1 SCID who underwent unconditioned marrow infusion from a matched unrelated donor after receiving third party VST therapy for adenovirus. Retransplantation utilizing the same donor after preconditioning chemotherapy was successful, suggesting that engraftment failure was not related to VST infusion and most likely related to the lack of conditioning chemotherapy before the first transplant(42)

Study Limitations to date

Though VST therapy has proved efficacious for treatment and prevention of viral infections in immunocompromised patients, there are still limitations moving forward. Few studies of VST therapy conducted thus far have included control groups,(17, 24) so it has been difficult to assess the true effect on survival rates. As studies move forward in the multicenter setting using multi-viral specific T-cells, the question of antigenic dominance when targeting a large number of viral antigens has been raised. Depending on the donor serostatus and HLA type, VST products may be heavily skewed to highly immunodominant viral antigens for one or

maybe two viruses. For example, CMV seropositive donors expressing B07:01 invariably have a robust response against CMV restricted through this HLA allele, which may account for a skewing of the expanded T-cell product to this single viral epitope.(45, 50) Viral specificity is also dependent upon pre-existing immunity in the donors. This, along with turn-around time to manufacture the VSTs, has led to the use of third party VSTs. However, as previously noted, these products are only partially HLA matched and are usually rejected within 3 months of administration.(37, 41) Given the lack of randomized, controlled trials, it is also difficult to fully assess the safety risks, including GVHD and CRS. The use of VSTs is promising, and addressing these study limitations will be important as the use of VSTs broadens applicability and becomes a treatment mainstay for refractory infections in the immunocompromised host.

FUTURE OF VST THERAPY FOR PIDD

The key future milestones for VST therapy in the PIDD patient population include widening availability and improving the breadth of pathogens that can be targeted. Studies to date have predominantly targeted DNA viruses such as CMV, EBV, and adenovirus. However, many other viruses are a potential threat to patients with profound PIDD. Respiratory viruses in particular are a danger, including RSV, human metapneumovirus, and human parainfluenza virus.(9, 51) T-cell epitopes for many of these viruses have been previously described,(52–54) and a current phase I trial is underway to test VST therapy targeting human parainfluenza virus-3. Among other potential targets, Human papilloma virus (HPV) is problematic in many PIDD patients with T-cell deficiencies, and is described even after HSCT in patients with X-linked and JAK3 deficient SCID.(55, 56) T-cell expansion targeting HPV proteins E6 and E7 has been successful from healthy donors, but has not been tested clinically to date.(57)

Many questions remain with respect to the differing manufacturing approaches for VST generation. Both primate and human studies have highlighted the importance of progenitor T- cell populations including central memory and stem cell memory subsets to maintain antigen- specific responses *in vivo*.(58–60) These populations are detectable in VST products at low percentages, but could potentially be enhanced using cell selection techniques or by modulating expansion conditions *in vitro*. For example, IL-21 and inhibitors of glycogen synthase 3b have both been described to maintain precursor T-cell populations.(61, 62) Hence, favoring these precursors could potentially improve persistence of VSTs *in vivo*.

Third party VST therapy holds great promise for extending availability of VSTs as an “off the shelf” therapeutic, but algorithms for best VST product selection in the HLA mismatched setting are not yet broadly established. Confirmation of the HLA restrictions which mediate antiviral activity however appears to be essential for antiviral activity.(36, 45) The stability of viral antigens in circulating viral isolates is also a critical factor for VST therapy, as an escape mutation has been described in the setting of adoptive immunotherapy targeting EBV.(63) Finally, as the number of targeted pathogens increases, it has been theorized that there may be an upper limit to the number of antigens that can be successfully targeted in a single T cell product due to antigenic competition. In studies published to date,

this has seemingly not been a major issue even targeting up to 5 viruses in a monoculture. However, it stands to reason that the number of cells targeting an individual antigen will be diluted by adding more antigens to a culture.

The cost of adoptive immunotherapy is another topic that has drawn much scrutiny, particularly with regard to chimeric antigen receptor (CAR) T cells.⁽⁶⁴⁾ At our institution, we have recently determined that the cost of manufacturing and testing a single VST product to be \$8500. This is comparable in cost to a course of many intravenous antiviral medications. Upon eventual approval, it is likely that the commercial cost will be higher, but as VSTs are not individualized products and do not require vector manufacturing or transduction, it is unlikely that third party VST banks will ever approach the cost of CAR T-cell therapy.

Administration of VSTs has been highly successful as a prophylactic and treatment strategy for high risk PID patients after HSCT. As we better define the effector and progenitor populations that are essential for adaptive immunity, modular transplantation is likely to represent the future of definitive therapy for PID, and VSTs will likely be an important tool in this field. An improved understanding of ideal viral targets and potential toxicities, particularly with the use of VSTs prior to HSCT, will be essential to further improve and expand adoptive T-cell therapy for patients with PID.

Acknowledgements:

We thank our patients and families for participation in this study, as well as the staffs of the Center for Cell and Gene Therapy, the Vaccine Research Center, and the Center for Cancer and Immunology Research. This work was supported by funding from the National Institutes of Health (U10HL108945–05 to HH/CB, an NIH Bench-to-Bedside award to HH/DD/AB/CB, K23-HL136783–01 to MDK), the Children's Cancer Foundation, and the Jeffrey Modell Foundation.

References

1. Bousfiha A, Jeddane L, Picard C, Ailal F, Bobby Gaspar H, Al-Herz W, et al. The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies. *J Clin Immunol*. 2018;38(1):129–43. [PubMed: 29226301]
2. Heimall J, Logan BR, Cowan MJ, Notarangelo LD, Griffith LM, Puck JM, et al. Immune Reconstitution and Survival of 100 SCID Patients Post Hematopoietic Cell Transplant: A PIDTC Natural History Study. *Blood*. 2017.
3. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000–2009. *N Engl J Med*. 2014;371(5):434–46. [PubMed: 25075835]
4. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. *Jama*. 2014;312(7):729–38. [PubMed: 25138334]
5. Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? *J Allergy Clin Immunol*. 2010;126(3):602–10 e1–11. [PubMed: 20673987]
6. Fox TA, Chakraverty R, Burns S, Carpenter B, Thomson K, Lowe D, et al. Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency. *Blood*. 2018; 131 (8):917–31. [PubMed: 29279357]

7. Hutsparidol S, Essa M, Richardson S, Schechter T, Ali M, Krueger J, et al. Significant Transplantation-Related Mortality from Respiratory Virus Infections within the First One Hundred Days in Children after Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2015;21(10):1802–7. [PubMed: 26117558]
8. Buckley RH. Transplantation of hematopoietic stem cells in human severe combined immunodeficiency: longterm outcomes. *Immunol Res*. 2011;49(1–3):25–43. [PubMed: 21116871]
9. Odek C, Kendirli T, Dogu F, Yaman A, Vatansever G, Cipe F, et al. Patients with primary immunodeficiencies in pediatric intensive care unit: outcomes and mortality-related risk factors. *J Clin Immunol*. 2014;34(3):309–15. [PubMed: 24510376]
10. Bollard CM, Heslop HE. T cells for viral infections after allogeneic hematopoietic stem cell transplant. *Blood*. 2016;127(26):3331–40. [PubMed: 27207801]
11. Walter EA, Greenberg PD, Gilbert MJ, Finch RJ, Watanabe KS, Thomas ED, et al. Reconstitution of cellular immunity against cytomegalovirus in recipients of allogeneic bone marrow by transfer of T-cell clones from the donor. *N Engl J Med*. 1995;333(16):1038–44. [PubMed: 7675046]
12. Papadopoulou A, Gerdemann U, Katari UL, Tzannou I, Liu H, Martinez C, et al. Activity of broad-spectrum T cells as treatment for AdV, EBV, CMV, BKV, and HHV6 infections after HSCT. *Science translational medicine*. 2014;6(242):242ra83.
13. Gerdemann U, Katari UL, Papadopoulou A, Keirnan JM, Craddock JA, Liu H, et al. Safety and clinical efficacy of rapidly-generated trivirus-directed T cells as treatment for adenovirus, EBV, and CMV infections after allogeneic hematopoietic stem cell transplant. *Mol Ther*. 2013.
14. Heslop HE, Slobod KS, Pule MA, Hale GA, Rousseau A, Smith CA, et al. Long-term outcome of EBV-specific T-cell infusions to prevent or treat EBV-related lymphoproliferative disease in transplant recipients. *Blood*. 2010;115(5):925–35. [PubMed: 19880495]
15. Leen AM, Christin A, Myers GD, Liu H, Cruz CR, Hanley PJ, et al. Cytotoxic T lymphocyte therapy with donor T cells prevents and treats adenovirus and Epstein-Barr virus infections after haploidentical and matched unrelated stem cell transplantation. *Blood*. 2009;114(19):4283–92. [PubMed: 19700662]
16. Leen AM, Myers GD, Sili U, Huls MH, Weiss H, Leung KS, et al. Monoculture-derived T lymphocytes specific for multiple viruses expand and produce clinically relevant effects in immunocompromised individuals. *Nat Med*. 2006;12(10):1160–6. [PubMed: 16998485]
17. Rooney CM, Smith CA, Ng CY, Loftin SK, Sixbey JW, Gan Y, et al. Infusion of cytotoxic T cells for the prevention and treatment of Epstein-Barr virus-induced lymphoma in allogeneic transplant recipients. *Blood*. 1998;92(5):1549–55. [PubMed: 9716582]
18. Heslop HE, Ng CY, Li C, Smith CA, Loftin SK, Krance RA, et al. Long-term restoration of immunity against Epstein-Barr virus infection by adoptive transfer of gene-modified virus-specific T lymphocytes. *Nat Med*. 1996;2(5):551–5. [PubMed: 8616714]
19. Rooney CM, Smith CA, Ng CY, Loftin S, Li C, Krance RA, et al. Use of gene-modified virus-specific T lymphocytes to control Epstein-Barr-virus-related lymphoproliferation. *Lancet*. 1995;345(8941):9–13. [PubMed: 7799740]
20. Ma CK, Blyth E, Clancy L, Simms R, Burgess J, Brown R, et al. Addition of varicella zoster virus-specific T cells to cytomegalovirus, Epstein-Barr virus and adenovirus tri-specific T cells as adoptive immunotherapy in patients undergoing allogeneic hematopoietic stem cell transplantation. *Cytotherapy*. 2015;17(10):1406–20. [PubMed: 26349000]
21. Blyth E, Clancy L, Simms R, Ma CK, Burgess J, Deo S, et al. Donor-derived CMV- specific T cells reduce the requirement for CMV-directed pharmacotherapy after allogeneic stem cell transplantation. *Blood*. 2013;121(18):3745–58. [PubMed: 23435462]
22. Micklethwaite KP, Clancy L, Sandher U, Hansen AM, Blyth E, Antonenas V, et al. Prophylactic infusion of cytomegalovirus-specific cytotoxic T lymphocytes stimulated with Ad5f35pp65 gene-modified dendritic cells after allogeneic hemopoietic stem cell transplantation. *Blood*. 2008;112(10):3974–81. [PubMed: 18768783]
23. Koehne G, Hasan A, Doubrovina E, Prockop S, Tyler E, Wasilewski G, et al. Immunotherapy with Donor T Cells Sensitized with Overlapping Pentadecapeptides for Treatment of Persistent Cytomegalovirus Infection or Viremia. *Biol Blood Marrow Transplant*. 2015;21(9):1663–78. [PubMed: 26028505]

24. Doubrovina E, Oflaz-Sozmen B, Prockop SE, Kernan NA, Abramson S, Teruya- Feldstein J, et al. Adoptive immunotherapy with unselected or EBV-specific T cells for biopsy- proven EBV+ lymphomas after allogeneic hematopoietic cell transplantation. *Blood*. 2012;119(11):2644–56. [PubMed: 22138512]
25. Sutrave G, Blyth E, Gottlieb DJ. Cellular therapy for multiple pathogen infections after hematopoietic stem cell transplant. *Cytotherapy*. 2017;19(11):1284–301. [PubMed: 28927824]
26. Gerdemann U, Keirnan JM, Katari UL, Yanagisawa R, Christin AS, Huye LE, et al. Rapidly generated multivirus-specific cytotoxic T lymphocytes for the prophylaxis and treatment of viral infections. *Mol Ther*. 2012;20(8):1622–32. [PubMed: 22801446]
27. Feucht J, Opherck K, Lang P, Kayser S, Hartl L, Bethge W, et al. Adoptive T-cell therapy with hexon-specific Th1 cells as a treatment of refractory adenovirus infection after HSCT. *Blood*. 2015; 125(12): 1986–94. [PubMed: 25617426]
28. Feucht J, Joachim L, Lang P, Feuchtinger T. Adoptive T-cell transfer for refractory viral infections with cytomegalovirus, Epstein-Barr virus or adenovirus after allogeneic stem cell transplantation. *Klin Padiatr*. 2013;225(3):164–9. [PubMed: 23700092]
29. Feuchtinger T, Opherck K, Bethge WA, Topp MS, Schuster FR, Weissinger EM, et al. Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation. *Blood*. 2010;116(20):4360–7. [PubMed: 20625005]
30. Feuchtinger T, Matthes-Martin S, Richard C, Lion T, Fuhrer M, Hamprecht K, et al. Safe adoptive transfer of virus-specific T-cell immunity for the treatment of systemic adenovirus infection after allogeneic stem cell transplantation. *Br J Haematol*. 2006;134(1):64–76. [PubMed: 16803570]
31. Creidy R, Moshous D, Touzot F, Elie C, Neven B, Gabrion A, et al. Specific T cells for the treatment of cytomegalovirus and/or adenovirus in the context of hematopoietic stem cell transplantation. *J Allergy Clin Immunol*. 2016;138(3):920–4 e3. [PubMed: 27246524]
32. Barker JN, Doubrovina E, Sauter C, Jaroscak JJ, Perales MA, Doubrovin M, et al. Successful treatment of EBV-associated posttransplantation lymphoma after cord blood transplantation using third-party EBV-specific cytotoxic T lymphocytes. *Blood*. 2010;116(23):5045–9. [PubMed: 20826724]
33. Vickers MA, Wilkie GM, Robinson N, Rivera N, Haque T, Crawford DH, et al. Establishment and operation of a Good Manufacturing Practice-compliant allogeneic Epstein- Barr virus (EBV)-specific cytotoxic cell bank for the treatment of EBV-associated lymphoproliferative disease. *Br J Haematol*. 2014;167(3):402–10. [PubMed: 25066775]
34. Haque T, Wilkie GM, Jones MM, Higgins CD, Urquhart G, Wingate P, et al. Allogeneic cytotoxic T-cell therapy for EBV-positive posttransplantation lymphoproliferative disease: results of a phase 2 multicenter clinical trial. *Blood*. 2007;110(4):1123–31. [PubMed: 17468341]
35. Haque T, Wilkie GM, Taylor C, Amlot PL, Murad P, Iley A, et al. Treatment of Epstein- Barr-virus-positive post-transplantation lymphoproliferative disease with partly HLA-matched allogeneic cytotoxic T cells. *Lancet*. 2002;360(9331):436–42. [PubMed: 12241714]
36. Tzannou I, Papadopoulou A, Naik S, Leung K, Martinez CA, Ramos CA, et al. Off-the- Shelf Virus-Specific T Cells to Treat BK Virus, Human Herpesvirus 6, Cytomegalovirus, Epstein- Barr Virus, and Adenovirus Infections After Allogeneic Hematopoietic Stem-Cell Transplantation. *J Clin Oncol*. 2017;35(31):3547–57. [PubMed: 28783452]
37. Leen AM, Bollard CM, Mendizabal AM, Shpall EJ, Szabolcs P, Antin JH, et al. Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation. *Blood*. 2013;121(26):5113–23. [PubMed: 23610374]
38. Withers B, Blyth E, Clancy LE, Yong A, Fraser C, Burgess J, et al. Long-term control of recurrent or refractory viral infections after allogeneic HSCT with third-party virus-specific T cells. *Blood Adv*. 2017;1(24):2193–205. [PubMed: 29296867]
39. Naik S, Nicholas SK, Martinez CA, Leen AM, Hanley PJ, Gottschalk SM, et al. Adoptive immunotherapy for primary immunodeficiency disorders with virus-specific T lymphocytes. *J Allergy Clin Immunol*. 2016.
40. Wynn RF, Arkwright PD, Haque T, Gharib MI, Wilkie G, Morton-Jones M, et al. Treatment of Epstein-Barr-virus-associated primary CNS B cell lymphoma with allogeneic T-cell

- immunotherapy and stem-cell transplantation. *The lancet oncology*. 2005;6(5):344–6. [PubMed: 15863383]
41. Uhlin M, Gertow J, Uzunel M, Okas M, Berglund S, Watz E, et al. Rapid salvage treatment with virus-specific T cells for therapy-resistant disease. *Clin Infect Dis*. 2012;55(8):1064–73. [PubMed: 22806594]
 42. Miller HK, Hanley PJ, Lang H, Lazarski CA, Chorvinsky EA, McCormack S, et al. Antiviral T Cells for Adenovirus in the Pretransplant Period: A Bridge Therapy for Severe Combined Immunodeficiency. *Biol Blood Marrow Transplant*. 2018.
 43. Cruz CR, Hanley PJ, Liu H, Torrano V, Lin YF, Arce JA, et al. Adverse events following infusion of T cells for adoptive immunotherapy: a 10-year experience. *Cytotherapy*. 2010;12(6):743–9. [PubMed: 20429793]
 44. Melenhorst JJ, Leen AM, Bollard CM, Quigley MF, Price DA, Rooney CM, et al. Allogeneic virus-specific T cells with HLA alloreactivity do not produce GVHD in human subjects. *Blood*. 2010;116(22):4700–2. [PubMed: 20709906]
 45. O'Reilly RJ, Prockop S, Hasan AN, Koehne G, Doubrovina E. Virus-specific T-cell banks for 'off the shelf' adoptive therapy of refractory infections. *Bone Marrow Transplant*. 2016.
 46. Hay KA, Hanafi LA, Li D, Gust J, Liles WC, Wurfel MM, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. *Blood*. 2017; 130(21):2295–306. [PubMed: 28924019]
 47. June CH, Sadelain M. Chimeric Antigen Receptor Therapy. *N Engl J Med*. 2018;379(1):64–73. [PubMed: 29972754]
 48. Papadopoulou A, Krance RA, Allen CE, Lee D, Rooney CM, Brenner MK, et al. Systemic inflammatory response syndrome after administration of unmodified T lymphocytes. *Mol Ther*. 2014;22(6):1134–8. [PubMed: 24651135]
 49. Qasim W, Derniame S, Gilmour K, Chiesa R, Weber M, Adams S, et al. Third-party virus-specific T cells eradicate adenoviraemia but trigger bystander graft-versus-host disease. *Br J Haematol*. 2011; 154(1):150–3. [PubMed: 21501134]
 50. Lacey SF, Villacres MC, La Rosa C, Wang Z, Longmate J, Martinez J, et al. Relative dominance of HLA-B*07 restricted CD8+ T-lymphocyte immune responses to human cytomegalovirus pp65 in persons sharing HLA-A*02 and HLA-B*07 alleles. *Hum Immunol*. 2003;64(4):440–52. [PubMed: 12651070]
 51. Crooks BN, Taylor CE, Turner AJ, Osman HK, Abinun M, Flood TJ, et al. Respiratory viral infections in primary immune deficiencies: significance and relevance to clinical outcome in a single BMT unit. *Bone Marrow Transplant*. 2000;26(10):1097–102. [PubMed: 11108309]
 52. McLaughlin LP, Lang H, Williams E, Wright KE, Powell A, Cruz CR, et al. Human parainfluenza virus-3 can be targeted by rapidly ex vivo expanded T lymphocytes. *Cytotherapy*. 2016.
 53. Tzannou I, Nicholas SK, Lulla P, Aguayo-Hiraldo PI, Misra A, Martinez CA, et al. Immunologic Profiling of Human Metapneumovirus for the Development of Targeted Immunotherapy. *J Infect Dis*. 2017;216(6):678–87. [PubMed: 28934427]
 54. McDermott DS, Knudson CJ, Varga SM. Determining the breadth of the respiratory syncytial virus-specific T cell response. *J Virol*. 2014;88(6):3135–43. [PubMed: 24371055]
 55. Leiding JW, Holland SM. Warts and all: human papillomavirus in primary immunodeficiencies. *J Allergy Clin Immunol*. 2012;130(5):1030–48. [PubMed: 23036745]
 56. Laffort C, Le Deist F, Favre M, Caillat-Zucman S, Radford-Weiss I, Debre M, et al. Severe cutaneous papillomavirus disease after haemopoietic stem-cell transplantation in patients with severe combined immune deficiency caused by common gammac cytokine receptor subunit or JAK-3 deficiency. *Lancet*. 2004;363(9426):2051–4. [PubMed: 15207958]
 57. McCormack SE, Cruz CRY, Wright KE, Powell Ab, Lang H, Trimble C, et al. Human papilloma virus-specific T cells can be generated from naive T cells for use as an immunotherapeutic strategy for immunocompromised patients. *Cytotherapy*. 2018;20(3):385–93. [PubMed: 29331266]
 58. Berger C, Jensen MC, Lansdorp PM, Gough M, Elliott C, Riddell SR. Adoptive transfer of effector CD8+ T cells derived from central memory cells establishes persistent T cell memory in primates. *J Clin Invest*. 2008;118(1):294–305. [PubMed: 18060041]

59. Roberto A, Castagna L, Zanon V, Bramanti S, Crocchiolo R, McLaren JE, et al. Role of naive-derived T memory stem cells in T-cell reconstitution following allogeneic transplantation. *Blood*. 2015; 125(18):2855–64. [PubMed: 25742699]
60. Cieri N, Oliveira G, Greco R, Forcato M, Taccioli C, Cianciotti B, et al. Generation of human memory stem T cells after haploidentical T-replete hematopoietic stem cell transplantation. *Blood*. 2015;125(18):2865–74. [PubMed: 25736310]
61. Orio J, Carli C, Janelle V, Giroux M, Taillefer J, Goupil M, et al. Early exposure to interleukin-21 limits rapidly generated anti-Epstein-Barr virus T-cell line differentiation. *Cytotherapy*. 2015;17(4):496–508. [PubMed: 25661862]
62. Sabatino M, Hu J, Sommariva M, Gautam S, Fellowes V, Hocker JD, et al. Generation of clinical-grade CD19-specific CAR-modified CD8+ memory stem cells for the treatment of human B-cell malignancies. *Blood*. 2016;128(4):519–28. [PubMed: 27226436]
63. Gottschalk S, Ng CY, Perez M, Smith CA, Sample C, Brenner MK, et al. An Epstein-Barr virus deletion mutant associated with fatal lymphoproliferative disease unresponsive to therapy with virus-specific CTLs. *Blood*. 2001;97(4):835–43. [PubMed: 11159505]
64. de Lima Lopes G, Nahas GR. Chimeric antigen receptor T cells, a savior with a high price. *Chin Clin Oncol*. 2018;7(2):21. [PubMed: 29764166]
65. Bao L, Cowan MJ, Dunham K, Horn B, McGuirk J, Gilman A, et al. Adoptive immunotherapy with CMV-specific cytotoxic T lymphocytes for stem cell transplant patients with refractory CMV infections. *J Immunother*. 2012;35(3):293–8. [PubMed: 22421947]
66. Punwani D, Wang H, Chan AY, Cowan MJ, Mallott J, Sunderam U, et al. Combined immunodeficiency due to MALT1 mutations, treated by hematopoietic cell transplantation. *J Clin Immunol*. 2015;35(2):135–46. [PubMed: 25627829]

Figure 1:

Methods of producing Virus-specific T-cells from peripheral blood mononuclear cells (PBMC) utilize either cell selection or *ex vivo* expansion. Selection utilizes either multimer sorting or immunomagnetic column selection to isolate VSTs after stimulation based on expression of interferon-gamma (Ifn-g) or CD154. *Ex vivo* expansion utilizes either antigen presenting cells (APCs) that have been transduced with viral antigens, or direct stimulation of PBMCs with viral peptide libraries to stimulate expansion of VSTs.

Table 1:

Demographics and Outcomes of PIDDD Patients in VSTs Studies.

Study	PIDDD Diagnosis	Infection(s)	VST Specificity	VST method	VST Source	Cell Dose	Outcomes
Bao et al.(65)	Hyper IgM Syndrome	CMV	CMV	Culture, peptide	HSCT donor, peripheral blood	5)10 ⁵ /kg	Persistent viremia
	SCID	CMV	CMV	Culture, peptide	HSCT donor, peripheral blood	5)10 ⁵ /kg	Resolution of viremia
	CID	CMV	CMV	Culture, peptide	HSCT donor, peripheral blood	2.5)10 ⁵ /kg	Resolution of viremia
Creidy et al.(31)	HLH	Meningo encephalitis; retinitis	AdV	Selection by IFN- γ secretion	Haploidentical HSCT donor, leukapheresis	1) 5)10 ⁴ /kg 2) 4 1.5)10 ⁴ /kg	Alive, stabilization of retinitis
	SCID	Meningo encephalitis; retinitis	AdV	Selection by IFN- γ secretion	Haploidentical HSCT donor, leukapheresis	1) 4 5)10 ⁴ /kg 2) 4 5)10 ⁴ /kg	Resolution of viremia; stabilization of retinitis
	HLH	Pneumonitis; encephalitis; retinitis; viremia	CMV	Selection by IFN- γ secretion	HSCT donor, leukapheresis	1.76)10 ⁴ /kg ⁸	Died at Day+3 (alveolar hemorrhage)
	HLH	CMV viremia	CMV	Selection by IFN- γ secretion	Haploidentical HSCT donor, leukapheresis	1) 4 3)10 ⁴ /kg ² 4 5.88)10 ⁴ /kg ³ 5 1.99)10 ⁵ /kg	Died at Day+96; pulmonary arterial hypertension
	CID	Retinitis	CMV	Selection by IFN- γ secretion	HSCT donor, leukapheresis	5)10 ⁴ /kg	Alive but blind
Feuch et al.(27)	HLH	Adenoviremia, diarrhea	AdV	Selection by IFN- γ secretion	HSCT donor, peripheral blood	5)10 ⁴ /kg	Clearance of AdV from blood and stool
Leen et al.(16)	SCID	Adenoviremia	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f-CMVpp65 vector	HSCT donor, peripheral blood	1)10 ⁸ /m ²	Clearance of AdV
Leen et al.(15)	SCID	Prophylaxis	EBV, AdV	Culture, LCL with Ad5f35 vector	HSCT donor, peripheral blood	1.35)10 ⁸ /m ²	Alive, no active infections
Gerdemann et al.(13)	HLH	CMV, AdV	CMV, EBV, AdV	Culture, peptide	HSCT donor, peripheral blood	2)10 ⁷ /m ²	CR
Papado- polou et al-(12)	LAD	Adenoviremia	CMV, EBV, AdV, HHV6, BK	Culture, peptide	Haploidentical HSCT donor, peripheral blood	2)10 ⁷ /m ²	CR
	GATA2	EBV, BK viremia	CMV, EBV, AdV, HHV6, BK	Culture, peptide	HSCT donor, peripheral blood	2)10 ⁷ /m ²	CR
	SCID variant	BK viremia; EBV viremia	CMV, EBV, AdV, HHV6, BK	Culture, peptide	HSCT donor, peripheral blood	2)10 ⁷ /m ²	CR
	HLH	HHV6, BK viremia	CMV, EBV, AdV, HHV6, BK	Culture, peptide	HSCT donor, peripheral blood	1)10 ⁷ /m ²	HHV6: CR; BK: NR; EBV: CR
1- 2)10 ⁶ /kg/d							

Author Manuscript

Study	PIDD Diagnosis	Infection(s)	VST Specificity	VST method	VST Source	Cell Dose	Outcomes
Dobrovina et al.(24)	XLP	Resolved EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/\text{m}^2$	No further EBV reactivation
	XLP	EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/\text{m}^2$	PR, Alive and well
	XLP	Resolved EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/\text{m}^2$	CR
	XLP	EBV-LPD with viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/\text{m}^2$	PR, Alive and well
	XLP-like	Resolved EBV viremia	EBV	Culture, LCL	HSCT donor, peripheral blood	$2 \times 10^7/\text{m}^2$	No further EBV reactivation
Uhlir et al.(41)	HLH	EBV-LPD	EBV	Culture, LCL	HSCT donor, peripheral blood	$1 \times 10^6/\text{kg} \times 3$ doses	PD; died
	XLP	EBV-LPD	EBV	Culture, LCL	Third Party	$1 \times 10^6/\text{kg} \times 3$ doses	CR
	ALPS	EBV-LPD	EBV	Culture, LCL	HSCT donor, peripheral blood	$1 \times 10^6/\text{kg}$	NE; died
Naik et al.(39)	SCID	CMV	CMV	Selection by HLA pentamer (CMV- pp65/ NLV)	Third-party (maternal, pretransplant)	$24.6 \times 10^4/\text{kg}$	PR, died
	IL7RA-SCID	Prophylaxis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f- CMVpp65 vector	HSCT donor, umbilical cord	$1.5 \times 10^7/\text{m}^2$	No viremia
	IL2RG-SCID	Prophylaxis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f- CMVpp65 vector	HSCT donor, umbilical cord	$2.5 \times 10^7/\text{m}^2$	No viremia
	IL2RG-SCID	Prophylaxis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f- CMVpp65 vector	HSCT donor, umbilical cord	$1 \times 10^7/\text{m}^2$	No viremia
	IL2RG-SCID	Prophylaxis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f- CMVpp65 vector	HSCT donor	$1 \times 10^7/\text{m}^2$	No viremia
	SCID	Prophylaxis	AdV	Culture, DC and LCL with Ad5f35 vector	HSCT donor	$1 \times 10^7/\text{m}^2$	No viremia
	MHC II deficiency	CMV viremia, pneumonitis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f- CMVpp65 vector	HSCT donor	$1 \times 10^7/\text{m}^2$	CR
	WAS	Prophylaxis	CMV, EBV, AdV	Culture, DC and LCL with Ad5f35f- CMVpp65 vector	HSCT donor	$1 \times 10^7/\text{m}^2$	No viremia
	CID, enterocolitis	Prophylaxis	EBV	Culture, peptide	HSCT donor	$2.5 \times 10^7/\text{m}^2$	No viremia

Study	PIDD Diagnosis	Infection(s)	VST Specificity	VST method	VST Source	Cell Dose	Outcomes
Miller et al.(42)	ADA-SCID SCID SCID	EBV-LPD CMV viremia CMV viremia, pneumonitis	CMV, EBV, AdV CMV, EBV, AdV CMV, EBV, AdV	Culture Culture Culture	Third party (pre-HSCT) HSCT donor HSCT donor (1 st dose), Third party (2 nd dose)	5×10 ⁶ /m ² 5×10 ⁶ /m ² /dose; 2 doses 1×10 ⁷ /m ² (1 st dose), 2×10 ⁷ /m ² (second dose)	NR, died from EBV-LPD PR, alive and well NR; died; refractory CMV and disseminated BCG
	MHC II Deficiency	Prophylaxis	CMV, EBV, AdV	Culture	HSCT donor	5×10 ⁶ /m ²	CMV: CR
	HLH (STXBP2)	CMV, EBV viremia	CMV, EBV, AdV	Culture	HSCT donor	1×10 ⁷ /m ² /dose × 2 doses	CMV: CR; EBV: CR
	WAS	Prophylaxis	CMV, EBV, AdV	Culture	HSCT donor	2×10 ⁷ /m ²	No viremia
	IL-10R deficiency	Adenoviremia, pneumonitis	CMV, EBV, AdV	Culture	Third Party	2×10 ⁷ /m ²	Adv: CR; CMV: CR
Punwani et al.(66)	HLH	EBV viremia	EBV	Culture	Third Party	2×10 ⁶ kg/d ose × 3 doses	EBV: PR; Died; PTLD
	CD4 lymphopenia	CMV viremia	CMV	Multimer selection	HSCT donor	2×10 ⁶ /kg	CMV: PR; died of fungal pneumonia
	SCID	Adenoviremia	CMV, EBV, AdV	Culture	Third party × 2 (pre-HSCT)	2×10 ⁷ /m ²	Adv: CR
	MALT1	CMV	CMV	Culture	HSCT donor	NA	CMV: CR
	Hyper IgM Syndrome	CMV	CMV	Culture	Third-party	2×10 ⁷ /m ² × 2 doses	CMV: CR
Withers et al.(38)	Hyper IgM Syndrome	CMV	CMV	Culture	Third-party	2×10 ⁷ /m ² × 2 doses	CMV: CR
	SCID	Adenoviremia	Adv	Culture	Third-party	2×10 ⁷ /m ²	Adv- CR
	SCAEBV	EBV	EBV	Culture	Third-party	2×10 ⁷ /m ²	PD, Died (Day+14)

Table abbreviations: CR: complete response; PR: partial response; NR: no response; PD: progressive disease; NA: Not available; NE: Not evaluated; DC: dendritic cells; LCL: lymphoblastoid cell line.