

compassionate use of immunoglobulins in our study was for neurologic diseases. This is similar to results of other studies.^{1-3,8} This is interesting because some of the neurologic diseases may have an autoimmune background.

Several other diseases are treated with immunoglobulins despite lack of scientific data, and this seems to be similar in our study as previously described.¹⁻³

Most of the children were treated for immune disorders or other approved indications. Our results seem to be in concordance with other reports.¹⁻³

Interestingly, more women than men received immunoglobulin therapy during the study period. This difference was largely related to more unapproved use in women. Although women have a higher incidence of many autoimmune diseases and neurologic disorders than do men, we do question whether this entirely explains this observed difference in the sex ratio. It is important to use immunoglobulin treatment cautiously but sensibly. Treatment with immunoglobulins is often very effective, but the cost can be high and must be taken into consideration. Unapproved use can certainly be accepted, but at the same time, the need for a better understanding of these diseases and the treatment is evident. It is hoped that research in the near future will facilitate this development.

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Bryndís Ester Ólafsdóttir, BSc^a
Davið Þór Þorsteinsson, MD^{b,c}
Rannveig Einarsson, MSc^{c,d}
Björn Rúnar Lúðvíksson, MD, PhD^{c,e}
Gerður Gröndal, MD^{c,f}
Kristján Erlendsson, MD^{c,e}
Ásgeir Haraldsson, MD, PhD^{a,b,c}

From ^athe Faculty of Medicine, University of Iceland, ^bChildren's Hospital Iceland, ^cLandspítali – University Hospital, ^dthe Division of Pharmaceutical Affairs, and the Departments of ^eImmunology and ^fMedicine, Landspítali – University Hospital, Reykjavík, Iceland. E-mail: asgeir@lsh.is.

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Haploidentical hematopoietic stem cell transplantation can lead to viral clearance in severe combined immunodeficiency

To the Editor:

Severe combined immunodeficiencies (SCIDs) are inherited T lymphocyte differentiation defects,¹ conventionally treated with hematopoietic stem cell transplantation (HSCT). For patients without an HLA-identical donor, T-lymphocyte-depleted (TCD) hematopoietic stem cell (HSC) transplantation from an HLA-mismatched donor is successful, with 75% to 87% survival.^{2,3} B-lymphocyte depletion reduces EBV-related lymphoproliferation. Various historical methods remove viable T lymphocytes, including *in vitro* anti-CD52 (CAMPATH-1M) antilymphocyte antibody, soy lectin, and sheep red blood cell rosetting. Recently, European centers performing TCD HSCT have been required to use CD34⁺ stem cell selection, most commonly the Miltenyi Clni-MACS system that uses an organic iron bead/anti-CD34 antibody conjugate to isolate purified CD34⁺ HSCs through a magnetic column.⁴ Although few remain, the residual viable T lymphocytes could cause graft-versus-host disease. The anti-CD52-treated product contains component blood cell precursors, cells in early differentiation, and stromal factors that aid HSC engraftment into the bone marrow niche.⁵ In a retrospective study, we suggested that better donor stem cell, myeloid, and B-lymphocyte engraftment is found in patients with SCID who received anti-CD52-depleted rather than CD34⁺-selected HSCs.⁶

In addition, by targeting T lymphocytes and B lymphocytes, CD3/CD19-depleted grafts retain CD34⁺ stem cells and engraftment-enhancing CD34⁺ progenitors and natural killer, dendritic, and graft-facilitating cells.⁷ Previous reports of CD3/CD19-depleted peripheral blood stem cell (PBSC) transplants are from patients with malignant disease.^{5,8,9}

Between 1999 and 2006, we transplanted 6 patients with SCID who had viral infections with CD34⁺ selected haploidentical grafts: 2 had cytomegalovirus (CMV), detailed in this report. Four were excluded, 2 with EBV, as the predominant issue during transplantation is B-lymphocyte proliferation; 1 died of preexisting brain-stem encephalitis on day 3, and the other developed B-lymphocyte proliferation treated with rituximab. One patient had human herpesvirus 6 in blood and bronchoalveolar lavage that resolved with foscarnet treatment pretransplant, and 1 patient with disseminated adenovirus died before engraftment. Since 2006, 4 patients with SCID have been transplanted by using haploidentical stem cells depleted of CD3/CD19⁺ cells, 3 with viral infections described in this report.

We describe immunoreconstitution and viral clearance in 5 patients: 2 received CD34-selected bone marrow prior to 2006 and 3 received CD3/CD19-depleted PBSCs⁵ after 2006. None had maternal engraftment.

TABLE I. Transplant characteristics

Patient Δ donor HLA match	Conditioning	Nucleated cells	CD34 ⁺	CD3	CD19
1 C γ C SCID Mother 3/6	Unconditioned	$4.5 \times 10^6/\text{kg}$	$2.7 \times 10^6/\text{kg}$	$1.8 \times 10^4/\text{kg}$	$1.1 \times 10^6/\text{kg}$
1 Mother	Unconditioned 2nd HSCT day 135	$1.4 \times 10^7/\text{kg}$	$0.82 \times 10^6/\text{kg}$	$4.0 \times 10^3/\text{kg}$	$2.9 \times 10^5/\text{kg}$
2 Atypical C γ C SCID Father 5/10	Alemtuzumab 0.3 mg/kg day 12 to day 14 Busulphan 16 mg/kg PO Cyclophosphamide 200 mg/kg	$7.8 \times 10^6/\text{kg}$	$3.5 \times 10^6/\text{kg}$	$1.2 \times 10^4/\text{kg}$	$1.7 \times 10^6/\text{kg}$
2 Father	Unconditioned 2nd HSCT day 102	$5.5 \times 10^6/\text{kg}$	$7.4 \times 10^6/\text{kg}$	$7.3 \times 10^4/\text{kg}$	$3.0 \times 10^5/\text{kg}$
3 SCID T-B ⁺ NK ⁺ Mother 7/10	Treosulfan 42 g/m ² Cyclophosphamide 200 mg/kg	$3.7 \times 10^8/\text{kg}$	$8.1 \times 10^6/\text{kg}$	$1.0 \times 10^5/\text{kg}$	$2.2 \times 10^4/\text{kg}$
4 SCID RAG 1 Mother 5/10	Treosulfan 36 g/m ² Cyclophosphamide 200 mg/kg	$4.2 \times 10^8/\text{kg}$	$8.8 \times 10^6/\text{kg}$	$6.0 \times 10^4/\text{kg}$	$6.7 \times 10^3/\text{kg}$
5 Atypical C γ C SCID Mother 6/10	Alemtuzumab 0.2 mg/kg day 12 to day 14 Treosulfan 36 g/m ² Fludarabine 150 mg/m ²	$8.4 \times 10^8/\text{kg}$	$8.6 \times 10^6/\text{kg}$	$2.9 \times 10^4/\text{kg}$	$1.7 \times 10^3/\text{kg}$

B, CD19⁺ lymphocytes; C γ C SCID, common gamma chain severe combined immunodeficiency; HIB, hemophilus B antibody response; N, in normal age-related range; NA, not applicable/available; NK, natural killer; PO, per os (by mouth); RAG, recombination activating gene; T, CD3⁺ lymphocytes; Tet, tetanus antibody response.

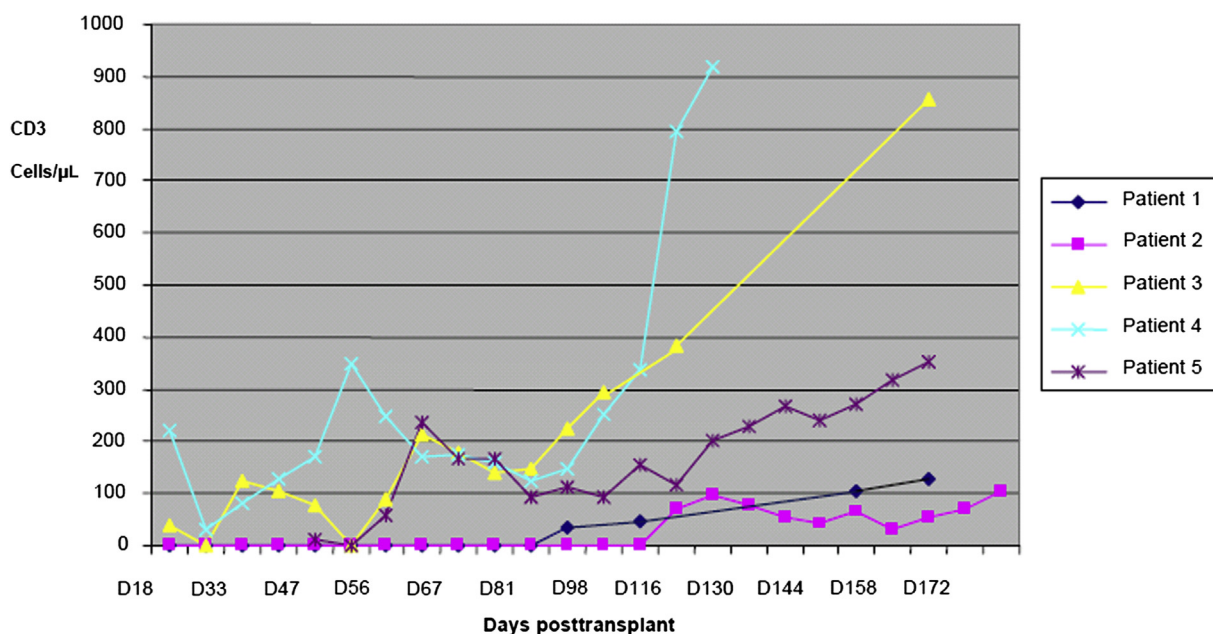
**FIG 1.** CD3 count with time post-HSCT for all patients.

TABLE I. (Continued)

Neutrophils >0.5 × 10 ⁹ /L	Time to T cells > 100 (day post- transplant)	Time to TEE	Time to viral clearance	Latest donor chimerism/length follow-up	Immune reconstitution
NA	—	—	—		
NA	+167/+33	+167/+33	+209/77	12 y T 100% B 0% CD15 0%	CD3 N CD4 N CD8 N CD19 N On immunoglobulin
+17	—	—	—	Whole blood 25%	
NA	—	—	Not cleared	T 95% B 12% CD15 3% Died day+253/151	Died
+11	+60	+117	+60	T 100% B 100% CD15 100% 3 y	CD3 N CD4 N CD8 N CD19 N Tet/HIB N
+ 10	+39	+80	+80	T 100% B 100% CD15 81% 28 mo	CD3 N CD4 N CD8 N CD19 N Tet/HIB N
+18	+60	+116	+97	T 100% B 100% CD15 100% 8 mo	CD3 Low CD4 Low CD8 Low CD19 Low On immunoglobulin

Pre- and post-transplant, upper respiratory tract secretions were screened weekly for respiratory viruses, stools for enteric viruses, and blood for surveillance monitoring for CMV, adenovirus, EBV, and human herpesvirus 6.

Conditioning was in accordance with the European Inborn Errors Working Party guidelines current at the time of transplantation. None had a suitable HLA-identical donor; all received manipulated parental HLA-haploidentical HSC. Of the 2 patients receiving CD34⁺ stem-cell–selected marrow, the clinical status of 1 precluded conditioning and patient 2 received busulfan and cyclophosphamide. Patients 2 and 5 with atypical presentation of *IL2RG*-deficient SCID received alemtuzumab from day 12 to day 14 from the graft to deplete recipient T lymphocytes. Sero-therapy may increase time to viral clearance and was omitted from the other 2 patients receiving CD3/CD19-depleted PBSCs.

Patients 3 to 5 transplanted with CD3/CD19-depleted PBSCs received treosulfan-based conditioning. All received cyclosporine anti-graft-versus-host disease prophylaxis aiming for levels of 50 µg/L. Patients 3 to 5 also received mycophenolate mofetil (Table I). Written consent was given.

Patient 1, aged 5 months, presented with respiratory syncytial virus (RSV) (treated with ribavirin and RSV-specific immunoglobulin), astrovirus, and calicivirus. CD3⁺ cells were less than 50/µL to day 114. He received an unconditioned boost infusion on day 135. He was discharged at 9 months post-transplant and remains well 12 years later.

Patient 2, with *Pneumocystis jiroveci* pneumonitis (PCP) and CMV at age 6 months, was transplanted from a CMV-positive donor. He received ganciclovir pretransplant and foscarnet from day 0. Cidofovir and ganciclovir were added to combat the increasing CMV load. He received methylprednisolone 1 to 2 mg/kg and weekly infliximab for pneumonitis. By day 81, CMV was barely detectable in blood by PCR, but chimerism was 25% donor with no T lymphocytes. Despite an unconditioned boost infusion, CMV remained intermittently detectable in blood and respiratory secretions and he succumbed to progressive respiratory failure day 253/151 post-transplant. Before death, he had 61 CD3⁺ cells/µL, but no thymic emigrant equivalents (TEE).

Patient 3, aged 8 months, presented with PCP and RSV. CD3⁺ cells were consistently more than 100 cells/µL by day 60, when

RSV cleared (Fig 1), with 103 TEE cells/ μ L by day 117. Weekly palivizumab supplemented intravenous immunoglobulin throughout the transplant. She maintains 100% donor chimerism at 3 years post-transplant, with full immunoreconstitution.

Patient 4, aged 6 months, was ventilated for PCP. Adenovirus was detected by using PCR in stool and blood immediately post-transplant and was treated with cidofovir. Fever and adenoviremia remitted by day 80. CD3⁺ cells were consistently more than 100 cells/ μ L from day 39 (see Fig E1 in this article's Online Repository at www.jacionline.org). At 28 months post-transplant, he has full immunoreconstitution.

Patient 5, aged 5.5 months, presented with PCP, rhinovirus, human metapneumovirus, and disseminated CMV. Ganciclovir pretransplant was substituted for foscarnet on day 0, when CMV in blood became negative. He developed fever from day 35 with irritability, orofacial dyskinesia, choreiform movements, brisk reflexes, and bilateral clonus. Cranial magnetic resonance imaging and electroencephalogram were normal. A high load of CMV was detected in the cerebrospinal fluid. For 6 weeks, ganciclovir 10 mg/kg was given twice daily to optimize cerebrospinal fluid penetration, with 3 doses of cidofovir. In addition, methylprednisolone 30 mg/kg treated the inflammatory reaction. The CMV titer diminished and was undetectable on day 97. Two hundred thirty-eight CD3⁺ cells/ μ L on day 60 decreased following immunosuppression with methylprednisolone but rose steadily from day 116 when TEE also began to appear. He appears neurologically normal at 8 months post-transplant with rising numbers of lymphocytes.

HLA-haploidentical donor transplants for SCID are diminishing as increasing numbers of cord-stem-cell-transplant procedures are performed.² However, children for whom no suitable donor is identified require an HLA-mismatched donor HSCT.

We report 5 virally infected patients with SCID who received anti-CD34⁺ stem-cell-selected marrow or CD3/CD19-depleted PBSC HSCT. T Lymphocytes appeared earlier in CD3/CD19-depleted recipients than in patients who received CD34⁺ selected stem cells, but both methods led to viral clearance and successful outcome. Our report further demonstrates that TCD transplants can quickly restore immunity to achieve viral clearance in patients with SCID. This is the first report of CD3/CD19-depleted grafts in infants with SCID that demonstrates rapid immunoreconstitution and viral clearance in 3 patients. Potential advantages of one method over another will need large prospective trials.

Mary Slatter, MD^{a,b}
Zohreh Nademi, PhD^a
Sanjay Patel, MD^a
Dawn Barge, PhD^c
Manoj Valappil, MD^d
Ken Brigham, MPhil^e
Sophie Hambleton, PhD^{a,b}
Julia Clark, MD^{a,b}
Terence Flood, MD^a
Andrew Cant, MD^{a,b}
Mario Abinun, DSc^{a,b}
Andrew Gennery, MD^{a,b}

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Less severe clinical manifestations in patients with hereditary angioedema with missense C1INH gene mutations

To the Editor:

Hereditary angioedema (HAE-C1INH) (OMIM#106100) caused by reduced level (type I) or impaired function (type II) of the C1 inhibitor (C1INH) is a rare disorder characterized by edematous attacks. The rate, location, and severity of recurring edemas are highly variable among patients.¹⁻³ In spite of repeated efforts aimed at clarifying the underlying causes of this heterogeneity, no definite explanation has been published yet. Thus, the aim of the current study was to analyze genotype-phenotype correlations in a well-characterized group of patients with HAE-C1INH.

The study population of 106 subjects of Caucasian origin, comprising 39 unrelated patients and their family members diagnosed with type I HAE-C1INH, included all patients followed up at the Hungarian HAE center from 2006 (see Table E1 in this article's Online Repository at www.jacionline.org). The annual numbers of attacks of different locations, as well as the number of ampoules of human plasma-derived C1INH concentrate (500 international units; Berinert; CSL Behring, Marburg, Germany) consumed over a year, were recorded for each patient for 5 years between 2006 and 2010. Besides the

From ^athe Department of Paediatric Immunology, ^bInstitute of Cellular Medicine, Newcastle University, ^cthe Regional Immunology Laboratory, ^dNewcastle upon Tyne Hospitals NHS Foundation Trust Health Protection Agency, and ^ethe Haematopoietic Stem Cell Laboratory, Newcastle upon Tyne, United Kingdom. E-mail: mary.slatter@nuth.nhs.uk.

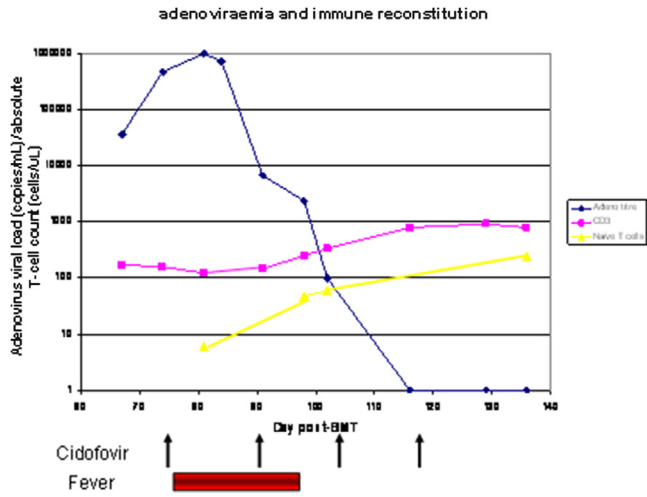


FIG E1. Adenoviraemia and immune reconstitution: Patient 4. *BMT*, Bone marrow transplantation.