

Outcome of boost haemopoietic stem cell transplant for decreased donor chimerism or graft dysfunction in primary immunodeficiency

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Summary:

Haemopoietic stem cell transplants (HSCT) cure increasing numbers of primary immunodeficiencies (PID): residual recipient T-cell function increases risk of incomplete or decreasing immune reconstitution, which may resolve following a second, unconditioned, infusion from the same donor (boost infusion). We assessed the outcome of 20 boost infusions in 19/139 patients transplanted for PID patients at our centre since 1987. Boost infusion was given 64–1226 days after the original HSCT. Follow-up was 4–124 months. In all, 12 of 19 patients cleared viral infection (6), or showed sustained increase in donor chimerism, T- and B-cell numbers and function, or other markers (6). In 7/12 patients, immunoglobulin replacement has been discontinued. Four were partially successful with stable low-level chimerism (two patients) or improved T-cell function, but not B cell function (two patients). Four failed with no change in donor chimerism or cell number. No significant association with donor source, T-cell depletion, conditioning regimen, boost infusion stem cell dose or time from original HSCT to boost was found. One patient developed grade III acute graft-versus-host disease despite cyclosporine, and one developed severe pneumonitis; both have recovered. Boost infusion was successful or partially successful in 84% of patients. The risk of adverse effects is low.

Bone Marrow Transplantation (2005) 35, 683–689.

doi:10.1038/sj.bmt.1704872

Published online 21 February 2005

Keywords: primary immunodeficiency; severe combined immunodeficiency; boost infusion; T-cell-depleted BMT; allogeneic BMT; slipping donor chimerism

Greatly improved survival rates enable cure by haemopoietic stem cell transplants (HSCTs) of an expanding number of primary immunodeficiencies (PID) including severe

combined immunodeficiency (SCID),¹ Wiskott–Aldrich syndrome (WAS),² CD40 ligand (CD40L) deficiency,³ X-linked lymphoproliferative disease (XLP),⁴ chronic granulomatous disease (CGD)⁵ and immunodeficiency polyendocrinopathy X linked (IPEX).⁶ As HSCT is attempted for PID with residual T-cell function, there is a greater risk of incomplete immune reconstitution or slipping donor chimerism.

The use of T-cell-depleted grafts in SCID increases the risk of graft failure,⁷ and in these cases, a second T-cell-depleted HSC infusion from the same donor without additional conditioning therapy (boost infusion) has been used to more fully reconstitute the immune system by adding additional stem cells to the marrow pool.⁸ Other risk factors for impaired graft function may be the increasing use of low-intensity conditioning regimens,⁹ inadequate number of infused haematopoietic stem cells,¹⁰ viral infections with CMV and HHV6,^{11–14} use of HLA-mismatched grafts¹⁵ and the use of post-HSCT immunosuppression to prevent graft-versus-host disease (GVHD). Attempts to improve chimerism include early stopping of cyclosporine prophylaxis for GVHD, augmentation by myeloid and erythroid growth factors, or performance of a complete second transplant with the risks of additional cytotoxic conditioning to the patient.

The role of a boost infusion is to increase haemopoietic stem cell engraftment in order to more fully reconstitute the immune system and consolidate cell lineages that are already engrafted, without the risk of additional chemotherapy. There are few data on the outcome of haematopoietic stem cell boost infusions without cytotoxic conditioning. One study reported nine boosts following T-cell-depleted haplo-identical transplants given for delay in the recovery of T-cell immunity associated with evidence of engraftment.⁸ Eight patients had SCID and one had aplastic anaemia. T-cell function, measured by T-cell numbers and mitogen responses improved, but there was no effect on B-cell immunity. A further study reported 20 boost infusions in patients with haematological malignancies or severe aplastic anaemia.¹⁶ Three of six patients who received boost infusions for primary graft failure engrafted, while 10 of 12 with secondary graft failure experienced improved graft function. Two patients with extensive haemolysis before the boost infusion temporarily improved.¹⁷ These findings are consistent with those of a further 15 of 20 patients with leukaemia or aplastic anaemia who engrafted after a boost infusion.¹⁸

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Received 30 September 2004; accepted 13 December 2004

Published online 21 February 2005

Techniques for the assessment of chimerism after HSCT have evolved. Short tandem repeat or variable number tandem repeat analyses of DNA give reproducible semi-quantitative data. PCR-based methods are more sensitive, enabling detection of minor populations of donor or recipient cells. PID have defects in different cell lineages (eg T cells in CD40L deficiency, neutrophils in CGD), and separation of cell lineages (eg by magnetic beads) enabling lineage-specific chimerism analysis ensures that donor chimerism in the cell line in question is accurately assessed. It is also useful after nonmyeloablative and reduced-intensity conditioning regimens where the early patterns of chimerism may predict the risks of graft loss or GVHD.

This single centre report is the first to assess the outcome of boost stem cell transplants for patients with other PID as well as SCID.

Patients and methods

All HSCT for PID in one of the UK's two national centres were reviewed. Since 1987, 139 children have been transplanted, 65 with SCID and 74 with other forms of PID. A total of 19 patients received 20 boost HSCTs from the original stem cell donor. Boost infusions were given for a decrease or absence of donor markers, poor T-cell function defined by PHA stimulation indices, poor B-cell function defined by the absence of endogenous IgG production and requirement for continued immunoglobulin replacement (IVIg) lack of specific antibody responses to immunisation, and persistent or recurrent viral infection.

A successful boost infusion was defined as resolution of the deficiency for which the boost was given. Partial success was defined as an improvement but not complete resolution of the deficiency. Failure of the boost infusion was defined as no improvement in the parameter for which the boost infusion was given.

The diagnoses of the children included eight with SCID and 11 with other PID (Tables 1–3). The conditioning regimens for the original HSCT included busulphan and cyclophosphamide, with or without the addition of Campath or antithymocyte globulin (ATG) (14 patients), Campath, fludarabine and melphalan (three patients), and no conditioning (two patients). No patients received radiotherapy. Seven patients received whole marrow for their original HSCT, four received marrow T-cell depleted *in vitro* with Campath and eight received CD34+ positively selected HSC using the Miltenyi-CliniMACS technique. The timing of the boost ranged from 64 to 1226 days post the original HSCT (median 266 days). No patient received cytoreductive chemotherapy immediately prior to the boost infusion, but two patients received serotherapy (one ATG (patient 19) and one Campath (patient 4)) to eliminate residual host immune mechanisms for marrow dysfunction. Only one (patient 10) received cyclosporine as GVHD prophylaxis for 6 weeks post boost infusion. All the remaining patients received no GVHD prophylaxis.

The length of follow-up ranged from 4 to 124 months (median 20 months). The success of the boost infusions was analysed with respect to underlying diagnosis, type of donor, whether the graft was T-cell depleted, conditioning

regimen for the original transplant, stem cell dose of boost infusion and time from original HSCT to boost infusion. The Mann–Whitney *U*-test was used to determine differences leading to success or failure of the procedure (GB-STAT™ version 6.5PPC, Dynamic Microsystems Inc.).

Results

The boost infusion was successful in 12 of 19 patients; one with T-negative, B-positive (T–B+) SCID required a second boost infusion, which was successful (patient 11, Table 2).

Viral clearance

Six patients cleared viral infections: small round structured virus (2), respiratory syncytial virus and astrovirus (1), cytomegalovirus (1), adenovirus (1), and Epstein–Barr virus (1) (Table 1).

Improved donor chimerism

In the remaining six patients who achieved a successful outcome, donor chimerism increased and or T- and B-cell numbers and function, or other markers such as neutrophil oxidative burst, CD40L expression, adenosine deaminase or purine nucleoside phosphorylase (PNP) levels showed a sustained increase. In seven of 12 patients, B-cell function has improved such that IVIg could be discontinued; a further two (patients 6 and 12) received rituximab and remain on IVIg until B-cell numbers normalise. The remaining three patients (patients 1, 9, and 13) who remain on IVIg are a year or less post boost infusion.

Patient 12 had cartilage hair hypoplasia with red cell aplasia and failure to thrive. She received CD34+ positively selected stem cells from an unrelated donor and developed pneumonitis associated with HHV6 infection, but made a good recovery. She had mixed chimerism with donor alleles only present in T cells and remained red cell transfusion-dependent 2 years post transplant. A bone marrow examination showed erythroid hypoplasia with active myelopoiesis and plenty of megakaryocytes. Owing to possible suppression of erythroid activity caused by persistent HHV6 infection, she received ganciclovir, foscarnet, and cidofovir, with no change in transfusion dependence. As the direct antiglobulin test was positive, she was treated for peripheral red cell destruction with high-dose IVIg (2 g/kg) and four doses of rituximab (375 mg/m²), but remained transfusion dependent. She received a boost infusion with PBSCs using CD34+ cell selection and after blood transfusions 2 and 5 weeks post procedure, she has not required any subsequent transfusions during the last 21 months. Her blood group has changed from recipient to donor confirming erythroid chimerism.

Failed and partially successful boost infusions

Four patients had partially successful boost infusions (Table 3); two have stable low level chimerism, and have

Table 1 Clinical characteristics of six patients with PID who cleared viral infection after boost infusion post-HSCT

Patient	Δ	Donor	Original conditioning regimen	Infection	Reason for boost infusion	Boost infusion stem cell source	CD34+ dose $\times 10^6$ /kg	Time to boost (days)	Outcome	F.U. from boost (months)	Chimerism
1	ICF	11/12 URD DQ MM	C1H Flu Mel	SRSV	WB chimerism* \downarrow 100 \rightarrow 15% T D = R WBC-T R > D	11/12 URD DQ MM	3.4	186	Success Cleared virus \uparrow chimerism	10	WB chimerism* \uparrow 83% T D > R B Dr WB-(T + B) D T chimerism** D WB-T chimerism** Rd
2	C γ C SCID	Mat haplo **TCD	Nil	RSV astrovirus	No donor alleles at 120 days	Mat haplo **TCD	0.82	134	Partial success Cleared virus No B cells	59	T chimerism** D WB-T chimerism** Rd
3	C γ C SCID	Pat haplo *TCD	Bu8 Cy200	CMV	Poor myeloid + plt engraftment – CMV WB chimerism** D	Pat haplo *TCD	N/A	294	Success Cleared virus	124	T chimerism** D B chimerism** D WB chimerism** D
4	CD40L def	URD 10/10	C1H Flu Mel	Disseminated Adeno	T chimerism** R WB-T chimerism** D	C1H URD 10/10	2.0	114	Success Cleared virus	24	T chimerism** D B chimerism** D WB chimerism** D CD40L expression normal
5	XLP	URD 11/12 DP MM	C1H Flu Mel	EBV PCR + ve	\downarrow T chimerism** D \rightarrow Rd \uparrow EBV viral load	URD 11/12 DP MM	3.9	245	Success EBV PCR –ve	24	T chimerism** R > D B chimerism** R > D WB chimerism** Rd
6	PNP SCID	URD 12/12	C1H Bu16 Cy200	SRSV	\downarrow PNP \downarrow T chimerism* 50% \rightarrow 15%	URD 12/12	5.0	246	Success Cleared virus	18	T chimerism* 52% T mixed, WB-T chimerism* R > D \uparrow PNP

Δ = diagnosis; ICF = immunodeficiency centromeric instability facial dysmorphism syndrome; C γ c = common gamma chain; SCID = severe combined immunodeficiency; CD40L def = CD40 ligand deficiency; XLP = X-linked lymphoproliferative disease; PNP = purine nucleoside phosphorylase deficiency; Pat = paternal; Mat = maternal; Haplo = haploidentical; *TCD = campath 1M *in vitro* T-cell depleted; **TCD = Miltenyi-CliniMACS CD34+ stem cell selection; URD = unrelated donor; MM = mismatched; Bu8 = busulphan 8 mg/kg; Bu16 = busulphan 16 mg/kg; Cy200 = cyclophosphamide 200g/kg; C1H = campath 1H 1 mg/kg; Flu = fludarabine 150 mg/m²; Mel = melphalan 140 mg/m²; SRSV = small round structured virus; Adeno = adenovirus; RSV = respiratory syncytial virus; CMV = cytomegalovirus; EBV = Epstein-Barr virus; \downarrow / \Rightarrow / \uparrow = falling/stabilised/rising; chimerism*/** = cytogenetic/molecular DNA chimerism; WB = white blood cells; T = T cells; B = B cells; D = donor; R = recipient; D > R = predominantly donor; R > D = predominantly recipient; d = trace of donor; r = trace of recipient. N/A = not available.

Table 2 Clinical characteristics of seven patients with PID with improved donor chimerism post-boost infusion following HSCT

Patient	Δ	Donor	Original conditioning regimen	Infection	Reason for boost infusion	Boost infusion stem cell source	CD34+ dose $\times 10^6/\text{kg}$	Time to boost (days)	Outcome	F.U. from boost (Months)	Chimerism
7	CGD	MSD	Bu16 Cy200	No	NOB \downarrow 91 \rightarrow 17% WB chimerism* \downarrow 47 \rightarrow 28%	MSD	4.3	265	Success NOB 32%	10	NOB \uparrow 32% WB chimerism* \uparrow 32%
8	ZAP 70	Mat haplo **TCD	Bu16Cy 200C1H	No	No CD8+ T cells T chimerism** D \rightarrow Rd WB chimerism** R	Mat haplo **TCD	4.2	126	Success \uparrow CD8 \uparrow chimerism	11	T Dr B dR WB-(T + B) dR
9	ADA SCID	Pat haplo **TCD	Bu16 Cy200	No	\downarrow ADA \downarrow T and B cells T chimerism** D > R WB chimerism** R > D	Pat haplo **TCD PBSC	60	474	Success \uparrow ADA \uparrow T cells \uparrow B cells	12	\uparrow ADA T chimerism** D > R B chimerism** R > D WB chimerism** R > D
10	CD40L def	URD **TCD	ATG Bu16 Cy200	No	\downarrow CD40L expression WB chimerism* 98 \rightarrow 50%	URD	5.5	1014	Success	27	WB chimerism* 100% CD40L expression normal
11a	T-B + SCID	Pat haplo *TCD	Bu8 Cy200	No	Splenectomy Loss of graft	1. Pat haplo *TCD	N/A	399	Ongoing BCG hepatitis \rightarrow further boost		T chimerism** d WB-T chimerism** R
11b						2. Pat haplo *TCD	N/A	245	Success	112	T chimerism** D B chimerism** R WB-(T + B) chimerism** 40%
12	CHH	URD **TCD	ATG Bu16 Cy200	HHV6 pneumonitis	T chimerism** DWB-T chimerism** ROngoing red cell aplasia	URD **TCD PBSC	7.7	927	Success	21	T chimerism** DWB-T chimerism** R > D Not Rbc dependent
13	WAS	URD **TCD 9/12 match (DR, C, D Q MM)	ATG Bu16 Cy200	No	\downarrow plt < 30 T chimerism* D > R B chimerism* R > D WB-(T + B) chimerism* Rd Plt mixed chimerism	URD **TCD PBSC	22	1226	Success Plt > 70	4	T chimerism* D > R B chimerism* R > D WB-(T + B) chimerism* R > D

Δ = diagnosis; CGD = chronic granulomatous disease; SCID = severe combined immunodeficiency; WAS = Wiskott-Aldrich syndrome; CD40L def = CD40 ligand deficiency; CHH = cartilage hair hypoplasia; ADA = adenosine deaminase deficiency; Pat = paternal; Mat = maternal; Haplo = haploidentical; *TCD = Campath 1M *in vitro* T-cell depleted; **TCD = Miltenyi-CliniMACS CD34+ stem cell selection; URD = unrelated donor; MSD = matched sibling donor; MM = mismatched; PBSC = peripheral blood stem cell; Bu8 = busulphan 8 mg/kg; Bu16 = busulphan 16 mg/kg; Cy200 = cyclophosphamide 200 mg/kg; C1H = Campath 1H 1 mg/kg; Flu = fludarabine 150 mg/m²; Mel = melphalan 140 mg/m²; ATG = antithymocyte globulin; HHV6 = human herpesvirus 6; \downarrow T cells = low T-cell numbers; NOB = neutrophil oxidative burst; $\downarrow/\Rightarrow/\uparrow$ = falling/stabilised/rising; chimerism*/** = cytogenetic/molecular DNA chimerism; WB = white blood cells; T = T cells; B = B cells; D = donor; R = recipient; D > R = predominantly donor; R > D = predominantly recipient; d = trace of donor; r = trace of recipient.

N/A = not available.

Table 3 Clinical characteristics of six patients with PID who underwent a partially successful or failed boost infusion post-HSCT

Patient	Δ	Donor	Original conditioning regimen	Infection	Reason for boost infusion	Boost infusion stem cell source	CD34+ dose $\times 10^6$ /kg	Time to boost (days)	Outcome	FU from boost (months)	Chimerism
14	CGD	MSD	Bu16 Cy200	No	NOB \downarrow 92 \rightarrow 15% WB chimerism* \downarrow 52 \rightarrow 33%	MSD	4.3	209	Partial success NOB 14%	10	NOB \Rightarrow 15% WB chimerism* \Rightarrow 22%
15	T-B- SCID	10/10 Pat	Nil	No	\downarrow T cells \downarrow PHA No B cells T chimerism** D	10/10 Pat	3.6	832	Partial success \uparrow T cells No Bs	76	T chimerism** D \uparrow PHA WB chimerism** Rd
16	CD40L def	URD 10/10 **TCD	ATG Bu16 Cy200	No	T chimerism** D D/r \rightarrow DR WB-T chimerism** DR \rightarrow R \downarrow CD40L expression	URD 10/10 **TCD	4.4	1056	Partial success Stable reduced CD40L expression	19	Stable but \downarrow CD40L expression T chimerism** Rd WB-T chimerism** Rd
17	RAG SCID	Pat. haplo *TCD	Bu8 Cy200	No	\downarrow T cells, absent PHA No B cells	Pat haplo **TCD	4.2	476	Failed \rightarrow 2nd BMT	—	
18	Artemis SCID	URD *TCD	Bu8 Cy200	Adeno	\downarrow T cells, No B cells	URD *TCD	1.2	267	Failed \rightarrow 2nd BMT	—	
19	RAG SCID	Pat. haplo **TCD	Bu16 Cy200 C1H	No	Acute rejection D + 19	ATG Pat haplo **TCD PBSC	13	64	Failed \rightarrow 2nd BMT	—	

Δ = diagnosis; RAG = recombinase-activating gene; CGD = chronic granulomatous disease; SCID = severe combined immunodeficiency; CD40L def = CD40 ligand deficiency; Pat = paternal; Haplo = haploidentical; *TCD = Campath 1M *in vitro* T-cell depleted; **TCD = Miltenyi-CliniMACS CD34+ stem cell selection; URD = unrelated donor; MSD = matched sibling donor; PBSC = peripheral peripheral blood stem cell; Bu8 = busulphan 8 mg/kg; Bu16 = busulphan 16 mg/kg; Cy200 = cyclophosphamide 200 g/kg; C1H = Campath 1H 1 mg/kg; ATG = antithymocyte globulin; adeno = adenovirus; \downarrow T cells = low T-cell numbers; PHA = phytohaemagglutination lymphocyte stimulation; NOB = neutrophil oxidative burst; $\downarrow/\Rightarrow/\uparrow$ = falling/stabilised/rising; chimerism*/** = cytogenetic/molecular DNA chimerism; WB = white blood cells; T = T cells; B = B cells; D = donor; R = recipient; D > R = predominantly donor; R > D = predominantly recipient; d = trace of donor; r = trace of recipient.

discontinued IVIG (patients 14 and 16), and two have improved T-cell numbers and function, but no donor B cells post boost infusion (patients 2 and 15). In these last two patients, the original HSCT was unconditioned. Four of the boost infusions failed with no increase in donor chimerism or cell number. In three, this was associated with T-negative, B-negative (T-B-) SCID and these patients went on to have a further conditioned HSCT.

There was no statistically significant association of outcome with donor source, T-cell depletion, conditioning regimen for the original transplant, stem cell dose of the boost infusion or time from original HSCT to boost infusion.

Complications following boost infusions

Complications were seen in two patients post boost infusion. The first patient PNP with deficiency (patient 6) received 12/12 HLA-matched unrelated donor marrow; no GVHD occurred after the original transplant. A whole marrow boost infusion was given without cyclosporine prophylaxis for GVHD, but the patient developed grade II skin GVHD on day +33 followed by severe pneumonitis requiring ventilation and high-dose immunosuppression. She required ventilatory support for 12 days, and received cyclosporine for 9 months, but at 18 months follow-up is well with good immune function and no GVHD.

The second patient with CD40L deficiency (patient 10) received CD34+ positively selected marrow stem cells from an unrelated donor with a single DP HLA mismatch in the first HSCT. For the boost infusion, whole marrow was used and cyclosporine given for 6 weeks as GVHD prophylaxis. After stopping the cyclosporine acute grade III GVHD developed involving skin and liver, successfully treated with steroids and cyclosporine, which were discontinued at 11 months post boost infusion. There has been no recurrence of GVHD and the patient remains free of GVHD 27 months post boost infusion.

Discussion

Increasing numbers of stem cell transplants show incomplete immune reconstitution.¹⁷ We have shown that patients with PID may benefit from a boost infusion, resulting in an increase in donor chimerism, clearance of persistent viral infection and improvement in T- and B-cell function. Furthermore, one patient has become red cell transfusion independent following a CD34+ positively selected stem cell boost infusion, with donor erythroid cell lines and another, with WAS, has a sustained increased in platelet count. We were surprised that a boost infusion with only CD34+ positively selected cells without conditioning was sufficient to achieve red cell chimerism and correct red cell aplasia.

The only association with failure of boost infusion was a diagnosis of T-B- SCID, although this was not statistically significant. However, of the four patients with T-B- SCID, three required a further stem cell transplant following cytoreductive conditioning and the fourth had only a partially successful boost. In that T-B- SCID is a

more difficult condition in which to achieve successful engraftment,¹ these results are not surprising.

The finding that GVHD after the boost infusion was uncommon confirms results of other studies.¹⁶ Only two patients who received whole marrow developed GVHD. No patients who received T-cell-depleted boost infusions developed GVHD. In the setting of haematological malignancy, a significant factor in HSCT is the GVL effect and therefore a limited amount of GVHD is frequently acceptable. Conversely, in the setting of PID, GVHD confers no advantage and therefore donor lymphocyte infusion (DLI) with the associated high risk of GVHD, particularly in an HLA-mismatched setting, was not used in this series of patients. Boost infusions with high doses of positively selected CD34+ stem cells may increase haematopoiesis without the risk of inducing GVHD or EBV-LPD in patients in whom transplant tolerance has already been achieved and in whom GVHD is not desirable. In all, 12 of the boost infusions (11 patients) received were T-cell-depleted boosts. In these patients, the use of DLI would have carried a high risk of GVHD.

Eight patients had viral infections, of whom six cleared the infection, one needed a further conditioned transplant and one remains persistently HHV6 positive by PCR. Viral clearance is likely to have been achieved by an improvement in T-cell function. In the six patients who cleared virus, two received TCD boost infusion; therefore, successful viral clearance was secondary to improved stem cell engraftment, rather than delivery of mature T cells in the donor stem cell product.

The source of stem cells did not affect outcome, although higher cell doses are achieved with the use of cytokine-mobilised peripheral blood HSC infusion. The overall benefit of peripheral cells compared to marrow cells for HSCT has not been established by long-term data, although the former will invariably result in a larger cell dose and more rapid early engraftment with the possibility of increased chronic GVHD.¹⁹

The timing of boost infusions was well in excess of the time needed for donor stem cell-derived T cells to mature in the thymus apart from possibly patients 2 and 8. The observed improvement in graft function is likely, therefore, to have been due to the increase in stem cells from the boost infusion, and not simply a function of improvement in the original graft that would have occurred whether or not a boost infusion had been performed.

Chimerism studies were not performed on bone marrow. Peripheral blood stem cells are generally more useful than bone marrow cells for chimerism analysis as chimerism of unsorted bone marrow cells correlates poorly with chimerism of T cells and cells of lineages other than the myeloid lineage.²⁰ After successful transplantation for WAS, a high rate of mixed haemopoietic chimaeras (30–50% of patients) has been observed sometimes associated with persistent thrombocytopenia.^{21,22} Sustained low platelet count after transplantation of unmanipulated nonidentical bone marrow has been corrected 10 years after the original transplant by a boost of CD133 positively selected stem cells.²³ In our patient with WAS (patient 13), the platelet counts increased from 3 weeks after the boost. Whether this was due to improved megakaryocyte lineage engraftment

or due to bystander effects of the boost infusion is unclear. In two patients^{2,15} who originally received unconditioned HSCT, the boost infusion led to an improvement in T-cell numbers, but donor B-cell engraftment was not achieved. In other series, the use of unconditioned HSCT in patients with SCID has also failed to achieve donor B-cell engraftment.⁷

The mechanism by which a boost infusion can increase donor chimerism in different cell lineages is not clear. In unconditioned transplants for SCID, T-cell engraftment is achieved more easily than B-cell engraftment.⁷ While the observed improvement in the majority of our patients may be due to improved T-cell function, we have also clearly documented improvements in engraftment of other cell lineages including neutrophils, red blood cells and platelets. Now that better techniques are available for cell separation and chimerism analysis, more studies are needed to better understand the effects of marrow microenvironment on the engraftment of different cell lineages. In conclusion, boost infusion was successful in 12 of 19 and partially successful in a further four patients (84%). Failure was associated with a diagnosis of T–B– SCID. The risk of adverse effects appears to be low.

Acknowledgements

We thank Dawn Barge at the Regional Immunology Laboratory, Newcastle upon Tyne NHS Trust for the lymphocyte phenotyping and Tony Jackson at the Northern Regional Genetics service for chimerism analysis.

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