Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency.

Running title: HSCT for adults with primary immunodeficiency

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KEY POINTS

1. Allogeneic HSCT with reduced intensity conditioning is safe and effective in younger adults with severe PID.

2. Referral triggers should include severe infections, autoimmunity, malignancy and disease progression despite conservative management.
ABSTRACT

Introduction The primary immunodeficiencies (PID), rare inherited diseases characterised by severe dysfunction of immunity have been successfully treated by allogeneic hematopoietic stem cell transplantation (Allo-HSCT) in childhood. Controversy exists regarding optimal timing and use of Allo-HSCT in adults, due to lack of experience and previous poor outcomes.

Materials and methods 29 consecutive adult patients, with a mean age at transplant of 24 years (range 17-50) underwent Allo-HSCT. Reduced intensity conditioning included Flu/Mel/Alemtuzumab (n=20), Flu/Bu/Alemtuzumab (n=8) and Flu/Bu/ATG (n=1). Stem cell donors were matched or mismatched unrelated (MUD/MMUD) (n=18) and matched related donors (MRD) (n=11). Overall survival, event free survival, transplant related mortality, acute and chronic GVHD incidence and severity, time to engraftment, lineage specific chimerism, immune reconstitution and discontinuation of immunoglobulin replacement therapy were recorded.

Results Overall survival (OS) at 3 years for the whole cohort was 85.2%. The rarer, non-CGD PID patients achieved an OS at 3 years of 88.9% (n=18), compared to 81.8% for CGD patients (n=11). Transplant related mortality (TRM) was low with only four deaths observed at a median follow-up of 3.5 years. There were no cases of early or late rejection. In all surviving patients either stable mixed chimerism or full donor chimerism were observed. At last follow-up 87% of the surviving patients had no evidence of persistent or recurrent infections.

Conclusion Allo-HSCT is safe and effective in young adult patients with severe PID and should be considered the treatment of choice where an appropriate donor is available.
INTRODUCTION

The primary immunodeficiencies (PID) are a rare group of inherited diseases characterised by severe dysfunction of adaptive and/or innate immunity, typically arising from genetic mutations in hematopoietic stem cells. Nearly 300 distinct immunodeficiencies have now been described, with 20 accounting for over 90% of cases. Excluding common variable immunodeficiency (CVID), three of the most common are severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome (WAS) and chronic granulomatous disease (CGD). Children with severe PIDs have been successfully treated by allogeneic hematopoietic stem cell transplantation (Allo-HSCT), which has been the major therapeutic option for inherited cellular immunodeficiency disorders since 1968.

However, almost all series published on outcomes for Allo-HSCT have focussed on pediatric patients. The median age at transplant of patients described in the largest published series are < 1 year for SCID, 2.8 years for WAS and 12.7 years for CGD, utilising reduced intensity conditioning (RIC).

Significant advances in hematopoietic transplantation over the past 20 years including refinement of HLA-tissue typing, adoption of RIC regimens, increased availability of alternative stem cell sources, improved methods of graft-versus-host disease (GvHD) prophylaxis and improved supportive care have translated into better outcomes today compared to the early experience.

Early Allo-HSCT is important in infants or children presenting with serious or life-threatening infections as without definitive treatment, patients with severe PID, such as SCID, rarely survive beyond 1 year of age. In addition, younger patients have less end-organ damage from repeated or severe infections. Indeed, overall survival has been shown to fall from 95% in SCID patients transplanted at ages less than 3.5 months to 76% in older children.

Whilst early Allo-HSCT is preferred for PID, this is often not possible. An initial milder clinical phenotype, delayed diagnosis, late presentation, lack of a genetic diagnosis or an inability to identify a suitable stem cell donor may result in patients surviving to adolescence and early adulthood without having undergone Allo-HSCT. Furthermore, in non-SCID forms of PID, the clinical phenotype can be very heterogeneous and 'atypical', largely due to the high number of genetic and functional defects affecting T, B and NK cells, neutrophils and/or antigen presentation. For these patients, diagnosis can be delayed or difficult and the natural history of exceptionally rare underlying diseases is often unclear. In several PIDs, controversy surrounding optimum timing of Allo-HSCT remains, due to rarity of disease, lack of experience, emerging gene therapies and infrequent published outcome data due to the very low numbers in any one centre.
One such disorder where optimum timing remains unclear is CGD, which is characterised by impairment of the phagocyte NADPH-oxidase complex. Patients with absent NADPH activity are one group thought to benefit from early transplant\textsuperscript{18} and criteria have been devised for Allo-HSCT in children. These are: life-threatening infection, non-compliance with antimicrobial prophylaxis or steroid-dependent autoimmune-inflammatory disease\textsuperscript{19}. In adolescents and adults, criteria are more difficult to apply due to higher rates of organ dysfunction and reported increased mortality from Allo-HSCT\textsuperscript{20}. The largest published case series reported a cohort of 70 CGD patients with excellent overall survival of 91.4% at median follow up (34 months), but this cohort had a median age of 8.9 years (interquartile range 3.8 to 19.3 years)\textsuperscript{10}. Similarly, the second largest series of 56 CGD patients also had an excellent overall survival of 93% at median follow up (21 months), but again the median age was young at 12.5 years\textsuperscript{9} with only 14 patients aged \( \geq 17 \) years of age.

There is even less experience of Allo-HSCT in rarer PID\textsuperscript{s} and the literature is confined to pediatric series or adult case reports. In the lethal genetic PID caused by GATA2 mutations, HSCT has resulted in reversal of the hematologic, immunologic and clinical phenotype in small series including adults\textsuperscript{21-22}. In addition, in XIAP deficiency, poor outcomes post Allo-HSCT have been reported, with high rates of transplant related mortality (TRM)\textsuperscript{23}, although a recent paper has described excellent outcome for 10 Japanese patients (all < 17 years) undergoing RIC conditioned HSCT\textsuperscript{24}.

Given the reduced toxicity of RIC regimens, these appear to be better tolerated in patients with PID who often have significant organ dysfunction and associated elevated haematopoietic cell transplant-comorbidity index (HCT-CI) scores\textsuperscript{25} pre-transplant. Elsewhere others have used low toxicity myeloablative conditioning regimens incorporating targeted treosulfan with excellent results in children\textsuperscript{26,27}.

We report here the outcome of 29 consecutive adult patients (\( \geq 17 \) years) who underwent Allo-HSCT for a variety of PID\textsuperscript{s} in the Allo-HSCT programmes of University College London Hospitals NHS Foundation Trust and the Royal Free London Hospital NHS Foundation Trust, UCL Centre for Immunodeficiency, July 2004 - November 2016. Prior to transplant all patients had developed complications that necessitated definitive treatment with curative intent. During the study period, 5 additional adult patients were referred for consideration of Allo-HSCT who did not proceed to transplant. Referral was triggered by life-threatening infection, malignancy, autoimmune or inflammatory phenomena, new genetic diagnosis or new donor availability.
METHODS

Study Design and Participants
All patients provided written consent as per institutional practice for Allo-HSCT. The mean age at transplant was 24 years (range 17-50 years). Of these, 11 patients had CGD and 18 had various other PID. Detailed patient demographics and transplant characteristics are shown in Table 1. Primary immunodeficiencies were diagnosed using international criteria. Patients with severe dysfunction of adaptive and/or innate immunity can present with recurrent infections, autoimmunity and/or malignancy. 19 patients had a genetic diagnosis and 10 had a combination of clinical phenotype with a corresponding functional defect. Secondary causes of immunodeficiency were excluded. Data on donor status, conditioning regimen, clinical condition during and after transplant and at last follow up was collected retrospectively from the medical notes and our Allo-HSCT database. The hematopoietic cell transplantation-comorbidity index (HCT-CI) is a comorbidity tool, which captures the prevalence, magnitude and severity of various organ impairments before Allo-HSCT in order to predict risk of transplant related mortality (TRM). HCT-CI scores pre-transplant were calculated for all patients\textsuperscript{22}. All patients had a score of ≥1 whilst 12 (41%) had a score of ≥3. HCT-CI scores were higher in the PID cohort (50% scored ≥3) compared to the CGD cohort (27% scored ≥3), which was not statistically significant (p=0.206), but may suggest an increased risk of TRM.

Stem Cell Source
11 patients had matched related donors (10 siblings, 1 10/10 matched paternal donor) and 18 had matched unrelated donors, including 5 with 1 antigen mismatched unrelated donors (4 A antigen mismatch, 1 C antigen mismatch). Patients and donors were matched for human leucocyte antigen (HLA) A, B, C, DRB1 and DQB1 by intermediate or high-resolution DNA-typing as appropriate. Mobilised peripheral blood stem cells (PBSC) were the stem cell source in 79% of the patients (n=23, including all non-CGD patients) whilst bone marrow was used in the other 21% (n=7, all CGD patients).

Allo-HSCT Conditioning Regimen
All patients were transplanted using previously described T cell-depleted (in vivo alemtuzumab or antithymocyte globulin, ATG) reduced intensity conditioning regimens\textsuperscript{9,28,29}. All non-CGD PID patients received fludarabine (30mg/m\textsuperscript{2} daily for 5 days), melphalan 140mg/m\textsuperscript{2} and alemtuzumab (100mg for MUD recipients delivered as 20mg OD, days -7 to day -3 and 30mg single dose on day -1 for MRD recipients after May 2010). Two of the early MRD patients also received 100mg alemtuzumab delivered as 20mg OD, days -7...
to day -3. Conditioning for CGD patients consisted of fludarabine (30mg/m² daily for 5 days), busulfan (1.6mg/kg twice daily for 3 days) or melphalan (140mg/m² total), together with alemtuzumab (0.2mg/kg daily for 3 days) for 10 patients or, in one patient, rabbit anti-thymocyte globulin (rATG) (2.5mg/kg daily for 3 days). The mean busulfan cumulative AUC was 56.05 (umol/L)(min) (range 44.34-62.66, n=7). Details are shown in Table 1.

In addition to antibody-mediated in vivo T cell depletion, GVHD prophylaxis with cyclosporine was used in all patients. Acute and chronic GVHD were graded as previously reported.

Supportive Care

Reverse isolation, antimicrobial and antifungal prophylaxis were used to reduce the risk of infectious complications. All patients received prophylaxis against Pneumocystis jiroveci and acyclovir prophylaxis against varicella zoster virus reactivation. Surveillance for cytomegalovirus (CMV), adenovirus (ADV) and Epstein Barr virus (EBV) infection was performed by weekly polymerase chain reaction or antigenemia testing, and pre-emptive treatment was administered according to institutional guidelines.

In patients who were receiving immunoglobulin replacement therapy prior to transplant this was continued until normal trough levels were demonstrated post transplant and the risk of further infectious complications was minimal.

Chimerism analysis

Chimerism samples were processed at 3-monthly intervals until 1 year post transplant and then 6 monthly or when indicated clinically (cytopenias, persistent infections, ongoing mixed chimerism). In patients with a sex-mismatched donor, chimerism was analysed by fluorescence in situ hybridization. In those with sex-matched donors, polymerase chain reaction of short tandem repeats was used. Lineage specific chimerism was performed on PBMC, T cell, B cell and granulocyte compartments. The laboratory reports results as follows; ‘donor’ where donor DNA ≥ 97%, ‘mixed’ where donor DNA ≥ 50% and <97%, ‘very mixed’ where there is more recipient than donor DNA (donor DNA ≥ 1% <50%) and ‘recipient’ where no donor DNA can be detected.

Study end points and statistical analysis

Data were analysed in April 2017, in accordance with published guidelines. Primary outcome measures were overall survival (OS), event free survival (EFS), transplant related mortality (TRM), neutrophil engraftment and platelet engraftment. OS was defined as the time from transplant to death from any cause. EFS was defined as the time from transplant to graft failure, graft rejection or death from any cause.
Probabilities of OS and EFS were calculated using the Kaplan-Meier method with SPSS 22.0 statistical package (SPSS, Chicago, IL, USA). Comparison of survival curves was made using the log-rank method. Cumulative incidence estimates were used to calculate TRM and engraftment of neutrophils (≥0.5x10⁹/L) and platelets (≥50x10⁹/L) was calculated using.

**RESULTS**

**Survival**

Overall survival of the whole cohort was 89.2% at 1 year and 85.2% at 3 years, with a mean follow up of 3.5 years (range 4 months – 12 years). Overall survival at 1 year was 90.9% and 77.9% at 3 years for MRD transplants (n=11) and 94.4% at 1 year and 88.9% at 3 years for M/MUD transplants, p=0.51 (n=18). Overall survival was 90.9% at 1 year and 81.8% at 3 years for CGD patients (n=11) and 94.4% at 1 year and 88.9% at 3 years for other PIDs, p=0.75 (n=18) (Figures 1A-1C).

Event-free survival for the whole cohort was 89.7% at 1 and 3 years (n=29), with no significant difference observed for EFS between MRD transplants and M/MUD transplants; 90.9% vs 88.9% respectively (p=0.73). There was no significant difference in EFS in patients with CGD and other PID; 90.9% vs 88.9% at 1 and 3 years (p=0.65) (Figures 1D-1F). One late death occurred in a patient over 9 years post transplant due to respiratory complications in the context of progression of pre-existing bronchiectasis.

**Engraftment**

There were no episodes of graft rejection or graft failure. For the whole cohort, neutrophil engraftment occurred after a median 12 days (mean 14, interquartile range 11-17) and median platelet engraftment was 14 days (mean 17, interquartile range 11-20). Comparing MRD to MUD/MMUD, median time to neutrophil engraftment was 11 (IQR 11-12) versus 15 (IQR 12-21) days respectively (Figure 2A). Comparing the two diagnostic groups, time to neutrophil engraftment was longer in patients with CGD (n=11), median 16 days (IQR 12-22) versus 11 days (IQR 11-14) in patients with other PIDs (n=18) (Figure 2B). The observed longer time to engraftment in the CGD group reflects the fact that 7 of 11 CGD patients had BM as the stem cell source compared to the non-CGD PID patients who all received PBSC.

Median time to platelet engraftment in MRD transplants was 12 days (IQR 11-21) and 18 days (IQR 12-21) in MUD/MMUD transplants (Figure 2C). Longer platelet engraftment was also seen in CGD patients, median 19 days (IQR 14-20) compared to 16 days (IQR 11-21) in patients with other PIDs (Figure 2D). None of the observed differences were statistically significant. One patient had a CD34+ selected stem cell top-up due to
persistent cytopenias, with good effect.

Transplant related mortality
Conditioning was generally well tolerated with no cases of interstitial pneumonitis, veno-occlusive disease or severe mucositis (grade III-IV). Transplant related mortality was low with only four deaths observed at a median follow-up of 31 months for the whole cohort (n=29) (Figures 3A-3C). Two patients died during the neutropenic phase, prior to engraftment, of multi organ failure secondary to sepsis (one had no active infection immediately prior to transplant and the other had chronic cholangiopathy and was on antimicrobial prophylaxis), one at 7 months post-transplant of granulomatous meningoencephalitis and a further patient at 28 months post transplant secondary to sepsis in the context of chronic extensive GVHD.

Graft versus host disease
13 patients developed grades I-II acute GVHD (10 skin only, 1 skin and gut, 1 gut only and 1 liver only) and one patient developed grade III aGVHD of the liver. Of these, 7 progressed to limited (single organ) chronic GVHD (4 skin only, 2 gut only and 1 pulmonary). A further patient developed steroid refractory extensive cGVHD. At last follow-up no patients had ongoing active cGVHD requiring systemic immune suppression.

Infectious Complications
A large proportion of patients had a high infectious burden pre-transplant as expected in patients with PID. Of the 29 patients, 24 (82%) had prior recurrent or severe infections, including recurrent bacterial infection (n=8), recurrent viral infection (n=7), both bacterial and systemic fungal infections (n=3), systemic fungal infection (n=2), both viral and bacterial infection (n=2), atypical mycobacterial infection (n=1) and combined viral and atypical mycobacterial infection (n=1). One patient had active pulmonary aspergilloma and three patients had ongoing HPV infection at the time of transplant (indicated in Table 1). Despite this, there was a distinct absence of major infection issues both intra and immediately post Allo-HSCT in our cohort. No patients suffered serious fungal infection post transplant, although azole prophylaxis was continued until off CSA in patients with pre-existing fungal infection (Table 2). No patients required granulocyte infusions. CMV reactivation was only observed in 6 patients (35% of at risk patients, defined as +/+ , -/+ or +/- recipient/donor pairs) and in all cases these responded to standard antiviral therapy. EBV reactivation with evidence of PTLD was observed in 4 patients all of whom responded completely to rituximab. An additional patient was treated with donor lymphocyte infusions (DLI) for presumed PTLD where no biopsy was available (n=1). No patient died of CMV, EBV or adenoviral infection.

Five patients had persistent viral warts pre-transplant with complete resolution or ongoing resolution of warts observed at last follow-up in two patients. In three patients, no improvement in warts was observed,
despite full donor T cell chimerism in all, including the two patients transplanted for DCML deficiency, who had pre-existing extensive perineal HPV-related intraepithelial neoplasia (VIN/CIN or AIN). A further patient with extensive confluent warts pre-transplant (NK deficiency) had persistent warts despite full reconstitution of T, B and NK cells.

At last follow-up the remaining 21 patients had no evidence of persistent or recurrent infections.

**Immune Reconstitution**

Lymphocyte subset analysis was performed on all the PID patients pre-transplant. Lymphocyte subset analysis was performed on all patients surviving beyond 3 months post-transplant (n=27) within the first 12 months post-transplant. Of the non-CGD PID patients (n=18), 13 of the 16 surviving PID patients had lymphocyte subset results at 12 months (3 had not reached 12 months follow up at the time of data collection). 70% of those with subset analysis performed (n=13) had achieved a normal lymphocyte count (1.0-2.8 x 10^9/L), 62% had normal absolute CD3+ cell counts (0.7-2.1 x 10^9/L), 62% normal CD4+ cell counts (0.3-1.4 x10^9/L) and 77% normal CD8+ cell counts (0.2-0.9 x10^9/L).

All CGD patients had normal neutrophil function tests post transplant (data not shown).

Of the 9 surviving patients who had been receiving monthly immunoglobulin replacement therapy pre-transplant, 89% were immunoglobulin-free at last follow up (Table 2).

**Chimerism**

Chimerism data was available for 23 of the 24 surviving patients at last follow up. At the time of analysis, 21 patients had results available at 12 months post transplant and 85% had full donor chimerism in unfractionated PBMCs. In the T cell fraction 52% of patients tested had achieved full donor chimerism at 12 months (Figure 4).

Multilineage full donor chimerism was observed in 10 (48%) of the patients with the rest showing mixed chimerism in at least one of the cell lineages tested. A trend to increasing chimerism stability with time was observed in our cohort. Chimerism was more robust in the B and myeloid cells compared to the T cell fraction. No correlation was found between mixed donor chimerism and age of patient, underlying diagnosis or donor type.

2 patients received DLI for persistent mixed chimerism (1 in the context of presumed PTLD with rising B cell numbers and FDG-avid lymphadenopathy on PET/CT scan). One achieved full donor chimerism in B cells and granulocytes with T cells remaining mixed and the other converted to full donor chimerism.

There were no cases of graft rejection and in all surviving patients either stable mixed chimerism or full donor chimerism were observed.
**PID-associated Colitis**

Of the 10 patients with moderate-severe inflammatory bowel disease pre-transplant (6 CGD, 1 XIAP, 1 CVID, 1 ALPS and 1 DCML deficiency), two died of TRM (both with CGD, patients 21 and 23) and the colitis has resolved in all 8 surviving patients, including the XIAP patient. No increased incidence of gut GVHD was observed in these patients.

**DISCUSSION**

We have demonstrated that in 29 young adult patients with high-risk primary immune deficiencies, reduced-intensity, *in vivo* T cell depleted Allo-HSCT was both effective and safe, with an overall survival of 85.2% at 3 years and a mean follow-up of 3.5 years (41 months). There was no significant difference in outcome between those undergoing matched related donor transplants and matched, or 1 antigen mismatched unrelated donor transplants (p=0.51). As predicted using our previously described T cell-depleting conditioning regimens, the observed cumulative incidence of severe acute GVHD incidence (grades III-IV) was very low at 6.5% and only 31% of patients developed chronic GVHD, symptoms which resolved allowing withdrawal of systemic immune suppression from 3 months post transplant in all but one of these patients. Full multilineage donor chimerism was achieved in 42% of patients, and all others achieved stable mixed chimerism. Larger studies are required to determine the degree of donor chimerism required post transplant for some of the rarer PIDS in order to achieve a functional cure. Good functional immune reconstitution was observed in all but one of the patients permitting the withdrawal of immunoglobulin replacement therapy post-transplant in 89% of patients. At last follow up 92% of surviving patients (n=24) were off immune suppression and the remaining two were in the process of weaning.

The overall and event free survival observed in this series of adult patients is comparable or better than that seen in published series of Allo-HSCT outcomes for pediatric and adolescent patients with PID and CGD. The patients in this study had not undergone Allo-HSCT earlier in life due to a variety of reasons including mild-moderate clinical phenotype in childhood therefore not precipitating referral, delay in diagnosis until adolescence/adulthood, late presentation, and/or lack of a suitable donor. Patients had subsequently developed complications that necessitated definitive treatment in the form of Allo-HSCT. Triggers for referral included life-threatening infection, malignancy, autoimmune or inflammatory phenomena, newly confirmed genetic diagnosis or new donor availability. Due to pre-existing organ dysfunction, ongoing infectious or
inflammatory phenomena all patients in this cohort had a HCT-CI of at least 1 whilst 12 had a score of 3 or greater predicting a higher than observed TRM. Both the HCT-CI score or European Group for Blood and Bone Marrow Transplantation (EBMT) score have been validated in patients with haematological malignancies and in paediatric populations. Neither score has been validated in patients with PID or specifically CGD however it provides validated information on the clinical condition of patients pre-transplant. Patients with cellular immunodeficiency have been shown to have a higher HCT-CI and this score is used most frequently in other published studies of HSCT in PID.

These promising results suggest that Allo-HSCT is safe when delivered in a specialist centre and should be considered as a potentially curative option for younger adult PID patients with an appropriate donor and a sufficiently severe clinical picture. We recommend proceeding to Allo-HSCT for adult patients with a known genetic diagnosis amenable to correction by transplantation, and where conservative management results in a shortened life expectancy and ongoing morbidity. The current widespread use of next generation sequencing is expected to facilitate earlier referral of eligible adults.
AUTHOR CONTRIBUTIONS
TF, SOB, KJT, SG and ECM collected the data and wrote the manuscript. All other authors provided clinical care for the patients described. All authors had access to the clinical and laboratory data. ECM had final responsibility for the decision to submit for publication.

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CONFLICT OF INTEREST DISCLOSURE
No author has a relevant conflict of interest to declare.
REFERENCES


**FIGURE TITLES AND LEGENDS**

**Figure 1. Probabilities of overall survival (OS) and event-free survival (EFS)**

(A) OS for the whole cohort was 89.2% at 12 months and 85.2% at 3 years (B) OS for matched related donors (MRD) 90.9% and 77.9% at 1 and 3 years respectively. OS for matched unrelated donors/mis-matched unrelated donors (MUD/MMUD) transplants was 94.4% and 88.9% at 1 and 3 years respectively, p=0.51. (C) OS for PID patients 94.4% and 88.9% at 1 and 3 years respectively. OS for adults for CGD patients was 90.9% and 81.8% at 1 and 3 years, p=0.75 (D) EFS 89.7% at 1 and 3 years. (E) EFS for MRD transplants 90.9% at both
1 and 3 years. EFS MUD/MMUD transplants 88.9% at 1 and 3 years, p=0.73 (F) EFS for PID patients 88.9%, EFS for CGD patients 90.9% at both 1 and 3 years, p=0.65.

Figure 2. Hematopoietic engraftment kinetics.
(A) Cumulative incidence of neutrophil engraftment (defined as >0.5\times10^9/L for 3 consecutive days). Median time to neutrophil engraftment was 11 days in matched related donor (MRD) transplants and 15 days in MUD/MMUD transplants. (B) Cumulative incidence of neutrophil engraftment in the two main diagnostic groups. Median time to neutrophil engraftment was 11 days in non-CGD PID patients and 16 days in CGD patients. (C) Cumulative incidence of platelet engraftment (defined as >50\times10^9/L for 3 consecutive days). Median time to platelet engraftment was 12 days in MRD transplants and 18 days in MUD/MMUD transplants. (D) Cumulative incidence of platelet engraftment in the two main diagnostic groups. Median time to platelet engraftment was 16 days in non-CGD PID patients and 19 days in CGD patients.

Figure 3. Cumulative incidence of transplant related mortality (TRM).
(A) Transplant related mortality (TRM) for all patients was 11% (n=29) at 1 year and 15% at 3 years. (B) TRM for patients with matched related donors (MRD) was 10% at 1 year and 22% at 3 years (n=11) vs 11% at 1 year and 3 years for MUD/MMUD transplants (n=18), p=0.536 (C) TRM for patients with CGD was 10% at 1 year and at 3 years (n=11) vs other PID 12% at 1 year and 3 years (n=18), p=0.73.

Figure 4: Peripheral blood chimerism post transplant.
(A) PBMC chimerism results at 3, 6 and 12 months (n = 20, 17 and 19 respectively): Full donor chimerism (≥97% donor DNA) was achieved in PBMC fraction in 71% at 3 months, 83% at 6 months and 85% at 12 months. (B) T cell chimerism results: full donor chimerism was achieved in the T cell fraction in 30% at 3 months, 41% at 6 months and 52% at 12 months. (C) B cell chimerism: Full donor chimerism was achieved in the B cell fraction in 65% at 3 months, 82% at 6 months and 69% at 12 months. (D) Chimerism in the granulocyte fraction. Full donor chimerism was seen in 83% patients at 3 months, 67% at 6 months and 67% at 12 months.
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<th>Diagnosis</th>
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<th>Age at HSCT/Sex</th>
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Autoimmune IPF

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<th>Medical Complications Prior to Transplant</th>
<th>HC-T2 Score</th>
<th>Donor (HLA mismatch)</th>
<th>Stem cell source</th>
<th>CBV dose</th>
<th>CMV Status</th>
<th>Conditioning Regimen</th>
<th>In vivo T-cell depletion (used)</th>
<th>GVHD Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-SCID</td>
<td>CSA</td>
<td>32</td>
<td>34/M</td>
<td>Incipient humplasma (HLH), autoimmune neutropenia, MGUS with IgG paraprotein, previous splenectomy, factor X deficiency.</td>
<td>1</td>
<td>MUD</td>
<td>PBC</td>
<td>6.7</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>Celiac in SCID</td>
<td>Co-confirmed by sequencing</td>
<td>1</td>
<td>26/m</td>
<td>FACs incidental and age related in therapy; Schizophrenia, recurrent infections, T cell leukaemia and pseudo-mumps, bronchocentric osteomyelitis with chronic cholangiopathy, refractory facial hair.</td>
<td>33</td>
<td>MUD</td>
<td>PBC</td>
<td>12.6</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>Absolute NK deficiency</td>
<td>Hypogammaglobulinaemia</td>
<td>No mutation identified</td>
<td>Whole genome sequencing pending.</td>
<td>14</td>
<td>27/m</td>
<td>Refractory paraprotein (IgE &gt;20), recurrent infection in, bronchileakage and pseudo-mumps, bronchocentric osteomyelitis with chronic cholangiopathy, refractory facial hair.</td>
<td>33</td>
<td>MUD</td>
<td>PBC</td>
<td>7.8</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
</tr>
<tr>
<td>T-Cell deficiency</td>
<td>CARS2 with tyrosine/oriental sequence reversion pending.</td>
<td>24</td>
<td>27/f</td>
<td>Thrombosis and MDS, bronchileakage, Crohn’s colitis, recurrent vital varats, Mycobacterium avium complex, and negative human latent virus.</td>
<td>33</td>
<td>MUD</td>
<td>PBC</td>
<td>6.3</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>All 112 RecF deficiency</td>
<td>Co-confirmed by sequencing</td>
<td>19</td>
<td>26/m</td>
<td>Refractory salmonella sepilis, salmonella percutis and salmonella percutis and salmonella percutis and salmonella percutis and salmonella percutis</td>
<td>33</td>
<td>MUD</td>
<td>PBC</td>
<td>7.6</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>Rag2/Red cell aplasia</td>
<td>HLA-B (13046-1) CYP2D6 (Gly35Val) heterozygous</td>
<td>16</td>
<td>20/m</td>
<td>Red cell aplasia, granulocytosis with lesions, high transfusion requirement and iron overload, chronic chronic NK cell proliferation, EBV-virion b.</td>
<td>33</td>
<td>MUD</td>
<td>PBC</td>
<td>5.4</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>X-linked IPF</td>
<td>Co-confirmed by sequencing</td>
<td>3</td>
<td>18/m</td>
<td>II cell NHL, hypogammaglobulinaemia.</td>
<td>1</td>
<td>MUD</td>
<td>PBC</td>
<td>11.0</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>Underlined CD1</td>
<td>CXXD2X mutation in CD27 gene</td>
<td>11</td>
<td>22/m</td>
<td>EBV-virion b, atypical stage 48 B cell rich II cell NHL, IFIH1 (B-CIOP 3 X), high dose IMx.</td>
<td>2</td>
<td>MUD</td>
<td>PBC</td>
<td>4.6</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>CD27 deficiency</td>
<td>CD27 B22.21286 (C111543) and SNP in exon 3 (3171N1387)</td>
<td>13</td>
<td>18/m</td>
<td>Nadir b sin splenectomy, EBV Stage II diffuse large B cell lymphoma.</td>
<td>1</td>
<td>MUD</td>
<td>PBC</td>
<td>6.4</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>Gata 2 deficiency</td>
<td>7q35-36/BCL2 Am at Akin States Patients</td>
<td>20</td>
<td>22/f</td>
<td>MDS, persistent vital varats, mild IgG hypogammaglobulinaemia, CD56, CD56 lymphopenia, EBV/CMV.</td>
<td>1</td>
<td>MUD</td>
<td>PBC</td>
<td>6.3</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>XAP deficiency</td>
<td>XIAP absent by FACs (2 centred) No mutation identified.</td>
<td>19</td>
<td>21/m</td>
<td>HIV, Crohn’s requiring paediatric myiasis a child.</td>
<td>33</td>
<td>MUD</td>
<td>PBC</td>
<td>4.7</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>Autoimmune IPF</td>
<td>D826T T cell mutation</td>
<td>2</td>
<td>21/f</td>
<td>Refractory Hodgkin’s lymphoma, autoimmune haemolytic, genital HSV, previous splenectomy, juvenile inflammatory arthropathy, polychondritis, lymphoproliferation,</td>
<td>2</td>
<td>MUD</td>
<td>PBC</td>
<td>2.1</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>Gata 2 mutation</td>
<td>Truncated duplication of the nucleotides not previously reported.</td>
<td>10</td>
<td>22/f</td>
<td>MDS with profound monocytopenia, prolonged severe EBV infection and herpesvirus and nodular necroplasia b.</td>
<td>33</td>
<td>MUD</td>
<td>PBC</td>
<td>2.0</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>XAP deficiency</td>
<td>Sequence variant c.497G&gt;A in exon 2 of hXAP gene. Not previously reported</td>
<td>4</td>
<td>24/m</td>
<td>EBV lymphoproliferative disease x2 episodes, hypogamaglobulinaemia, splenomegaly, polymyalgia rheumatica, inflammatory myopathy, IIM, rheumatologic arthritis.</td>
<td>2</td>
<td>MUD</td>
<td>PBC</td>
<td>5.5</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Mel</td>
<td>CSA</td>
</tr>
<tr>
<td>A2-GGCD</td>
<td>P477 deficiency identified in FACs a relapse</td>
<td>18</td>
<td>19/m</td>
<td>Refractory infection including 3a pyrophosphatase b.</td>
<td>1</td>
<td>TdT 30/30</td>
<td>BM</td>
<td>3.7</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Bu</td>
<td>CSA</td>
</tr>
<tr>
<td>A2-GGCD</td>
<td>P477 deficiency identified in FACs a relapse</td>
<td>18</td>
<td>19/m</td>
<td>Refractory infection, chronic relapsing multi-locosseous lili, multi-locosseous infection n. infection.</td>
<td>2</td>
<td>MUD</td>
<td>PBC</td>
<td>2.1</td>
<td>+/-</td>
<td>11/10 (0.6mg/kg)</td>
<td>Fu Bu</td>
<td>CSA</td>
</tr>
<tr>
<td>CGD Type</td>
<td>Diagnosis</td>
<td>Age/SEX</td>
<td>#</td>
<td>FD</td>
<td>FD SNP/Change</td>
<td>Leukopenia</td>
<td>Recurrent Infections</td>
<td>BM Status</td>
<td>BM Source</td>
<td>Grafting Method</td>
<td>CSA</td>
<td>ATG</td>
</tr>
<tr>
<td>----------</td>
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<td>----</td>
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<td>-----------</td>
<td>----------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>X-linked CGD</td>
<td>CYBB intron6 ggt&gt;atg (MCLeod phenotype)</td>
<td>19/F</td>
<td>1</td>
<td>MUD</td>
<td>BM</td>
<td>3.6</td>
<td>-/-</td>
<td>Flu / Bu</td>
<td>Alemizumab</td>
<td>(100mg)</td>
<td>CSA</td>
<td>2</td>
</tr>
<tr>
<td>X-linked CGD</td>
<td>NCF1 (c.579G&gt;A (Trp193*))</td>
<td>21/F</td>
<td>1</td>
<td>MUD</td>
<td>BM</td>
<td>3.9</td>
<td>-/-</td>
<td>Flu / Bu</td>
<td>Alemizumab</td>
<td>(100mg)</td>
<td>CSA</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 1: Patient demographics and transplant characteristics.

CVID: common variable immunodeficiency; LDLP: lymphoproliferative disease; SCID: severe combined immunodeficiency; NK: natural killer cell; DCML: dendritic cell, monocyte, B lymphocyte, and natural killer lymphocyte deficiency; AR: autosomal recessive; CID: combined immunodeficiency; XAPI: X-linked inhibitor of apoptosis protein deficiency; CGD: chronic granulomatous disease; APDS2: Activated PI3Kδ syndrome type 2; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; MRD: matched related donor; PBSC: peripheral blood stem cells; BM: bone marrow; CSA: cyclosporin A; Flu: fludarabine; Bu: busulfan; Mel: melphalan; rATG: rabbit anti-thymocyte globulin; FACs: fluorescence-activated cell sorting; HCT–CI: hematopoietic cell transplant comorbidity index; R/D: recipient/donor CMV sero status; *: active infection at transplant; $: unresolved viral warts at transplant.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Acute GVHD (grade)</th>
<th>Chronic GVHD</th>
<th>CMV Status (f/u)</th>
<th>Infectious Complications</th>
<th>Other complications</th>
<th>Days FU</th>
<th>Present Status</th>
<th>Immuno- Suppression at lastFU (Y/N)</th>
<th>Immuno globulin replacement (Continues, Off or N/A)</th>
<th>Peripheral Blood Chimerism at lastFU (RBMCA)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CVID</td>
<td>N/A</td>
<td>N/A</td>
<td>+/+</td>
<td>Sepsis.</td>
<td>Multorgan failure.</td>
<td>12</td>
<td>Dead.</td>
<td>Y</td>
<td>N/A</td>
<td>Died TRM (sepsis).</td>
</tr>
<tr>
<td>6</td>
<td>Cyclic SCID</td>
<td>N/A</td>
<td>N/A</td>
<td>+/+</td>
<td>Sepsis.</td>
<td>Multorgan failure.</td>
<td>7</td>
<td>Dead.</td>
<td>Y</td>
<td>N/A</td>
<td>Died TRM (sepsis).</td>
</tr>
<tr>
<td>14</td>
<td>Gata2 deficiency</td>
<td>None.</td>
<td>-/+ Permanent pernicious anemia with VHL.</td>
<td>None.</td>
<td>None.</td>
<td>None.</td>
<td>1051</td>
<td>Alive.</td>
<td>N</td>
<td>N/A</td>
<td>Full donor chimerism.</td>
</tr>
<tr>
<td>15</td>
<td>XLP deficiency</td>
<td>None.</td>
<td>-/+ Warts left foot and right index finger resolving.</td>
<td>None.</td>
<td>None.</td>
<td>None.</td>
<td>629</td>
<td>Alive.</td>
<td>N</td>
<td>N/A</td>
<td>Stable mixed chimerism (mixed all lineages).</td>
</tr>
<tr>
<td>16</td>
<td>Autoimmune</td>
<td>Limited (skin).</td>
<td>-/+ CMV reactivation</td>
<td>None.</td>
<td>None.</td>
<td>None.</td>
<td>118</td>
<td>Alive.</td>
<td>N</td>
<td>N/A</td>
<td>Chimerism pending.</td>
</tr>
<tr>
<td>20</td>
<td>ABCG2</td>
<td>None.</td>
<td>-/+ None.</td>
<td>None.</td>
<td>None.</td>
<td>None.</td>
<td>971</td>
<td>Alive.</td>
<td>N</td>
<td>N/A</td>
<td>Stable mixed chimerism (full donor in PMN and B cells, mixed in T cell and granulocyte fractions).</td>
</tr>
<tr>
<td>21</td>
<td>ABCG2</td>
<td>None.</td>
<td>-/+ Bilateral lower limb eschar and involvement of no other organs identified.</td>
<td>None.</td>
<td>None.</td>
<td>None.</td>
<td>210</td>
<td>Dead.</td>
<td>Y</td>
<td>N/A</td>
<td>Full donor chimerism.</td>
</tr>
<tr>
<td>22</td>
<td>Varieity of CVID</td>
<td>Grade 1 skin.</td>
<td>-/+ None.</td>
<td>None.</td>
<td>None.</td>
<td>None.</td>
<td>992</td>
<td>Alive.</td>
<td>N</td>
<td>N/A</td>
<td>Stable mixed chimerism (full donor in B cell fraction, mixed in other lineages).</td>
</tr>
<tr>
<td></td>
<td>X-linked CGD</td>
<td>Grade</td>
<td>Skin</td>
<td>Steroid refractory, extensive</td>
<td>Multiple infective complication metastated with immune suppression for GVHD</td>
<td>Y</td>
<td>N/A</td>
<td>Died TRM (steroid refractory extensive COVD)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>X-linked CGD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>6/6</td>
<td>Dead</td>
<td>N/A</td>
<td>Full donor chimerism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>X-linked CGD</td>
<td>Non</td>
<td>Non</td>
<td>Non</td>
<td>Non</td>
<td>18/8</td>
<td>Alive</td>
<td>N</td>
<td>Stable mixed chimerism (in line in all lineages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>X-linked CGD</td>
<td>Grade 1</td>
<td>Skin</td>
<td>Non</td>
<td>Non</td>
<td>1001</td>
<td>Alive</td>
<td>N</td>
<td>Full donor chimerism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>X-linked CGD</td>
<td>Grade 1</td>
<td>Skin</td>
<td>Limited</td>
<td>Limited</td>
<td>13/19</td>
<td>Alive</td>
<td>N</td>
<td>Stable mixed chimerism (in line in all lineages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>X-linked CGD</td>
<td>Grade 1</td>
<td>Skin</td>
<td>Limited</td>
<td>Limited</td>
<td>18/7</td>
<td>Alive</td>
<td>N</td>
<td>Stable mixed chimerism (in line in all lineages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>X-linked CGD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>35/16</td>
<td>Alive</td>
<td>N</td>
<td>Stable mixed chimerism (in line in all lineages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>X-linked CGD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>69/7</td>
<td>Alive</td>
<td>N</td>
<td>Stable mixed chimerism (in line in all lineages)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Transplant outcome and resolution of PID-related complications.**

GVHD graft versus host disease; R/D recipient/donor CMV sero status; FU follow up; TRM transplant related mortality; ITP idiopathic thrombocytopenic purpura; DLI donor lymphocyte infusion; PTLD post transplant lymphoproliferative disease; HPV human papilloma virus; AIN/VIN/CIN anal/vaginal/cervical intraepithelial neoplasia; EBV Epstein Barr virus; MC mixed chimerism; ICSI intracytoplasmic sperm injection; N/A Not applicable; Full donor ≥97% donor DNA; Mixed chimerism ≥ 50% < 97% donor DNA; * See Figure 4 for lineage specific chimerism.
Figure 1. Probabilities of overall survival (OS) and event-free survival (EFS).
Figure 2. Haematopoietic engraftment kinetics.
Figure 3. Cumulative incidence of transplant related mortality (TRM).
Figure 4: Chimerism Kinetics