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Allogeneic Haematopoietic Stem Cell Transplantation for Systemic Onset Juvenile Idiopathic Arthritis

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Background: Some patients with systemic juvenile idiopathic arthritis (sJIA) experience a severe disease course with destructive arthritis which is refractory to conventional therapy including the "biologics," and/or develop life threatening complications such as macrophage activation syndrome (MAS). This group of patients has been considered for allogeneic hematopoietic stem cell transplantation (HSCT). The aim of this study was to examine the outcome of patients undergoing allogeneic HSCT for sJIA.

Methods: 8 patients (4 female) with sJIA underwent allogeneic HSCT at 3 UK transplant centers between 2007 and 2014. All patients were refractory to standard therapy (n=4), had failed autologous HSCT (n=1), or developed secondary HLH/MAS poorly responsive to treatment (n=3). Median age at transplant was 8.9 years (range 2 - 16 years). All received reduced toxicity conditioning regimens: Fludarabine, Melphalan, Alemtuzumab (n=6) or Treosulfan, Fludarabine, Alemtuzumab (n=2). All patients received peripheral blood stem cell grafts: from a 10/10 HLA matched unrelated donor (n=5), 9/10 HLA mismatched unrelated donors (n=2) and matched sibling (n=1). Patients received Cyclosporin (CsA) and mycophenolate mofetil (MMF) for graft-vs-host disease (GVHD) prophylaxis (n=5), CsA alone (n=2) and 1 patient received Sirolimus and MMF due to previous CsA toxicity.

Results: Seven out of 8 patients are alive with median follow-up of 16 months (range 4 - 56 months); one patient who had a previous unsuccessful autologous HSCT died of severe metabolic acidosis and hyperglycaemia following an orthopedic procedure 20 months post successful mismatched unrelated donor HSCT. Four patients achieved full donor chimerism in all cell lineages and 4 (including both those who received Treosulfan-based conditioning) achieved high levels of mixed donor chimerism in all lineages. One patient had grade II and 1 patient had grade IV acute GVHD. With the use of Alemtuzumab in already heavily immunosuppressed patients, viral reactivation was observed in most, some with a more severe disease course (BK encephalitis; HHV6 enterocolitis). All patients had significant improvement of arthritis (Fig 1), reduction of ESR (Fig 2), resolution of MAS and improved quality of life following allogeneic HSCT; all achieved complete drug-free remission of JIA at last follow-up.

Conclusion: Allogeneic HSCT using Alemtuzumab and reduced toxicity conditioning appears to be an effective therapeutic option for patients with systemic onset JIA which is refractory to conventional therapy and/or complicated by MAS. Long term follow up is required to ascertain whether disease control continues indefinitely.

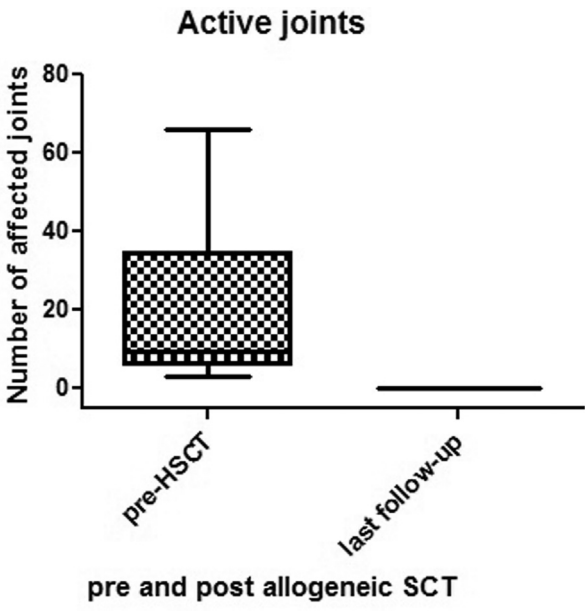

Figure 1.

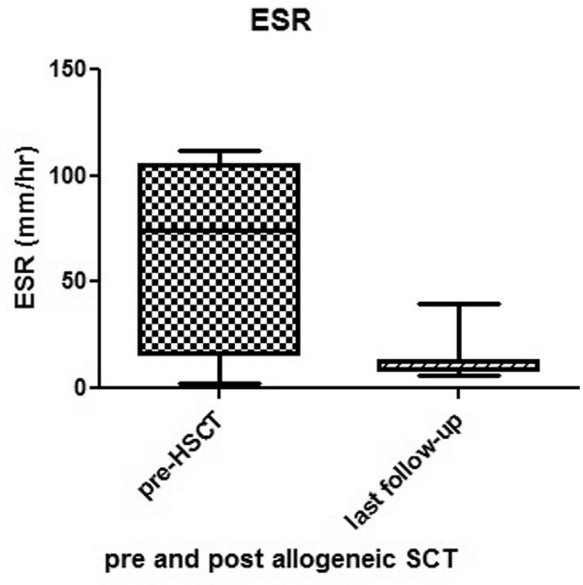

Figure 2.

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Induction of Durable Mixed Hematopoietic Chimerism and Immune Tolerance in Monkeys

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Mixed hematopoietic chimerism is a promising approach to achieving transplantation tolerance. Transient mixed hematopoietic chimerism leads to renal allograft tolerance in about 70% of cynomolgus monkeys when the kidney is co-transplanted with MHC-mismatched bone marrow (BMT). This same approach failed to achieve tolerance with more immunogenic organs such as lungs and hearts. Murine studies have demonstrated that the addition of regulatory T cells (Tregs) to BMTs using a non-myeloablative protocol (that is insufficient to allow engraftment), permits lasting mixed chimerism, BM engraftment and skin graft tolerance. We aim to extend this approach into the pre-clinical cynomolgus monkey model.

We have developed a protocol for the expansion of (100 million-1 billion) host polyclonal cynomolgus macaque Tregs (pTregs) (CD4+, CD25hi, CD127-/lo, FoxP3+). Cryopreserved Tregs are thawed and washed prior to infusion on days 0, 2, 5, 7 and (+/-) 50 to recipients conditioned with total body irradiation (1.25-1.5cGy) on days -6 and -5, thymic irradiation (7Gy) on day -1, ATGAM on days -2, -1 and 0, anti-CD40L on days 0, 2, 5, 7, 9 and 12 and cyclosporine or rapamycin (monotherapy) for 30 days (from day -2 to day 28 after BMT). To assess for tolerance, a skin or kidney allograft from the same donor was grafted four months post-BMT, after discontinuation of all immunosuppression.

Control animals (which did not receive Tregs (n=4) lost chimerism within 40 days. In vitro, anti-donor proliferative responses were observed, and donor kidneys were rejected. In contrast, animals that received Tregs together with BMT (n = 2) developed remarkably high and long-lasting chimerism, with a peak of >90% in myeloid lineages and range of 110-335 days. Unfortunately, experimental animals that reactivated CMV early after BMT either succumbed to CMV viremia or lost the BM graft when treated with myelotoxic antivirals. The substitution of rapamycin for CyA allowed control of early CMV reactivation (n=3 animals) and boosted the number of Tregs in the peripheral blood. T cell chimerism was observed only in Treg recipients, with high CD31 expression, suggesting new thymic emigrants. Tregs animals were donor-hyporesponsive 7 weeks post-BMT. One animal received a kidney graft on day +120 which was accepted without immunosuppression until euthanasia on day 335 (without evidence for histopathological rejection and with normal kidney function). The second Treg recipient received skin grafts on day 119. The third party graft is suspected to be rejected (histopathology to be confirmed) within 7 days and the donor skin is visually healthy three weeks post-transplant.

In summary, host pTregs given at the time of BMT across MHC barriers prolongs donor chimerism up to 335 days (extending it beyond 60 days for the first time in 20 years using this protocol) without GVHD and allows for the survival of donor organs transplanted four months post-BMT.

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Health-Related Quality of Life Among Older Adult Related Hematopoietic Stem Cells (HSC) Donors (>60 yrs.) Is Equivalent to or Better Than That of Younger Adult Related Donors (18-60 yrs.)

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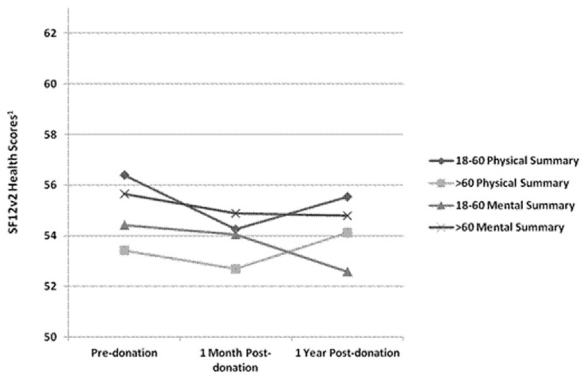
It is critical to understand HRQoL among older related siblings who are increasingly asked to donate HSC. Findings presented here are from a 5 year study of related donor (RD) safety and HRQoL (RDSafe). The goal was to compare HRQoL in older vs. younger adult RD.

Participants were older adult RD (ages >60 yrs; median=65 yrs; n=105) and younger adult RD (ages 18-60; median=42 yrs; n=59) who donated PBSC at domestic U.S. centers between 3/2010 and 4/2013. Data were collected via structured telephone interviews at pre-donation, and 4 weeks and 1 year post-donation. Interviews focused on socio-demographics, physical and mental health, and donation-related perceptions using well-validated instruments including the SF-12v2 to assess general physical/mental health. Odds ratios for dichotomous variables t-tests for continuous variables and mixed linear models were used to examine age group differences.

Demographics: Older RD were less likely to be employed, and more likely be white, married, and to have children. **Pre-donation**: Pre-donation, older RD had poorer physical health (t=-3.28; p<.01) but did not differ from younger RD on psychosocial variables including general mental health, depression, and anxiety. There were no group differences in ambivalence, satisfaction, or medical concerns about donation although older RD were more likely to consult their physician about donation (OR=13.18; p<.001). Older RD had fewer work/family concerns (t=-2.04; p<.05). **Post-donation**: 4 weeks post-donation, there were no group differences in general physical health, mental health, or any of 12 donation-related symptoms. Older RD were less likely to report donation-related pain (t=-2.29; p<.05) and continued to have fewer work/family concerns about the donation process (t=-3.39; p<.01). At 1 year post-donation, there were no differences in general physical and mental health or in the percent of RD reporting feeling completely back to normal. There was a nonsignificant trend for older RD to report a longer recovery period (t=1.78; p=.08). Older RD reported fewer current problems sleeping (OR=0.39; p<.05) but did not differ from younger RD on any other symptoms or in concern about longer-term donation effects. Mixed linear models (Figure 1) indicated that older RD had poorer physical health



[1]Ware JE, Jr, Kosinski M, Turner-Bowker DM, Gandek B. How to Score Version 2 of the SF-12® Health Survey (With a Supplement Documenting Version 1), Lincoln, RI: Quality Metric Incorporated, 2002.

Figure 1. Longitudinal physical and mental health status of older and younger adult related PBSC donors.