Delayed but Successful T Cell Immune Reconstitution Following Umbilical Cord Blood Transplantation Conditioned with Thymoglobulin alone in IL-7Rα-mutated SCID

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October 3, 2022

Δελαψεδ βυτ Συϲϲεϲϲφυλ Τ ἓλλ Ιμμυνε Ρεϲονστιτυτιον Φολλοωινγ Υμβιλιϲαλ ὃρδ Βλοοδ Τρανσπλαντατιον ὃνδιτιονεδ ωιτη Τηψμογλοβυλιν αλονε ιν ΙΛ-7Ρα-μυτατεδ Σ"ΙΔ

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Conflict of Interest Statement: Authors declare no conflict of interest and no funding for this manuscript

Word count (main Text): 840

Tables: 0

Figures: 1

Supplemental files: 0

References: 13

Key words : IL-7Rα-mutation SCID, Thymoglobulin, umbilical cord blood transplant, Covid-19 infection, delayed T-cell recovery

Running title : T cell reconstitution in IL-7Rα-mutated SCID after UCBT

Abbreviations	Full phrase
SCID	Severe combined immunodeficiency disorder
IL-7Rα	Interleukin-7 receptor-alpha
HSCT	Hematopoietic stem cell transplantation
IVIG	Immunoglobulin
HLA	Human leukocyte antigen
UCBT	Umbilical cord blood transplantation
TREC	T cell receptor excised circles
rATG	Rabbit anti-thymocyte globulin
GvHD	Graft versus host disease
RTE	Recent thymic emigrant population
STR	Short tandem repeat

To the Editor,

Severe combined immunodeficiency disorder (SCID) due to mutation in interleukin-7 receptor-alpha (IL-7Rα) gene resulting in B+NK+ phenotype can be successfully treated with hematopoietic stem cell transplantation (HSCT) [1, 2]. NK+ SCID cases have been challenging due to risk of graft rejection mediated by NK cells. We report an outcome of a baby with IL-7Rα-mutated SCID who underwent umbilical cord blood transplantation (UCBT) with anti-thymocyte globulin alone conditioning.

A male patient with B+NK+ SCID secondary to homozygous *IL7R* α exon 1 deletion underwent UCBT at 3 months of age. There was no evidence of maternal engraftment. Matched sibling or unrelated donors were not available, and parents opted UBCT over haploidentical SCT. The patient received molecularly HLA 7/8-matched (C allele mismatch) UCBT at a total nucleated cell dose of $15.6x10^8$/kg and CD34+ dose of $2.43x10^6$/kg conditioned with Thymoglobulin® (rabbit anti-thymocyte globulin) (rATG) at a total dose of 7.5mg/kg (days -4 thru -2). For graft versus host disease (GvHD) prophylaxis, he was given mycophenolate mofetil (days 0- thru +35) and tacrolimus day -3 through day +57 at which time he had no evidence of engraftment.

Due to lack of any T cell recovery at 4 months post-UCBT, keeping the possibility of UCB donor T cell depletion from rATG in mind, proceeding with a second transplant option was debated. However, he was noted to have evidence of T cell recovery (absolute CD3+ count of 98 cells/mcL with 6.6% CD4+ naïve T cells) five months post-UCBT, which continued to improve over time.

Engraftment and immune reconstitution were monitored by flow cytometric immune profiling and recent thymic emigrant population (RTE) determination characterized by CD31+/CD4+ naïve T cells, T cell receptor excision circles (TREC) analysis, short tandem repeat (STR) studies in myeloid and lymphoid populations, serum immunoglobulin levels and mitogen response assessments (Figure 1). Serum IgA and IgM levels were detected at 16 and 83 mg/dl, respectively on day +183. Absolute lymphocyte counts, T cell numbers, RTE percent and serum IgG, IgA, IgM levels all increased and reached normal levels by day +273; last intravenous immunoglobulin (IVIG) supplementation was on day +183. While myeloid chimerism

was 0%, B-cell donor chimerism increased progressively to a maximum of 41% and NK cells at 21% donor chimerism on day +217 post UCBT. Following T-cell recovery, the patient maintained full donor chimerism in T cells (98% on day +518). Interestingly, higher CD5-dim T cell percent, seen during early days of RTE observation; however, had declined later. T cells have shown almost normal mitogen responses at day+248 (Figure 1). Subsequently, anti-microbial prophylaxis was discontinued. The patient is now 25 months post-UCBT and is doing well. He did not develop GvHD. He has been growing and developing age-appropriately and has started childhood immunizations.

This is the first reported case of a successful UCBT for IL-7Rα-mutated SCID conditioned with rATG alone. The patient achieved full donor T cell chimerism along with normal quantitative and qualitative T and B cell function. Our experience suggests that conditioning with rATG in the setting of UCBT may lead to delayed T cell recovery likely due to*in-vivo* presence of rATG at the time of UCBT infusion leading to depletion of T cells in the UCB graft. Admiraal *et al.* also showed that T cell reconstitution was dependent on ATG exposure in children undergoing UCBT [6, 7]. During the initial months following HSCT, T cell reconstitution is dependent on homeostatic peripheral expansion of graft T cells. *In-vivo* graft T cell depletion by ATG adversely impacts homeostatic peripheral expansion. Thymopoiesis is established around 4-6 months post-HSCT and subsequently contributes to T cell reconstitution. In our patient, T cell recovery along with presence of RTE was noted at 5 months post-UCBT, which is consistent with recovery through thymopoiesis. Based on our experience, it may be prudent to consider a lower dose or earlier administration of rATG in the setting of UCBT for SCID to deplete host rather than non-primed cord blood T and NK cells.

One of the advantages of using UCB in the treatment was higher likelihood of B cell engraftment and decreased need for long term IVIG [9] [3], also in contrast to T cell depleted haploidentical and matched unrelated bone marrow transplants [10] [11]. Other advantage of using UCBT in SCID is lower risk of transmitting infections and viral reactivation following engraftment [12], which has been a problem with unrelated donor or TCRαβ-depleted haploidentical HSCT as well as with alemtuzumab conditioning [3, 5, 13].

In a T cell–depleted graft, circulating T cells may not be detected for several months after transplantation [14]; which might increase the risk of infection. However, our patient did relatively well with anti-microbial prophylaxis. As reported previously, T cell-depleted UCBT may have a superior B cell engraftment in IL-7Rα-mutated SCID [9] paralleling our experience as mixed chimerism was observed in the B-cell lineage along with normal serum immunoglobulin levels without supplementation. In conclusion, UCBT with modified ATG conditioning can be an acceptable alternative in IL-7Rα-mutated SCID cases when HLA-matched sibling donor or newly advanced graft T cell depletion strategies are not available [6, 7].

Statements and Declarations

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

The first draft of the manuscript was written by Eman Al-Antary and Süreyya Savaşan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The patient data summarized in the current report are available from the corresponding author on reasonable request.

Ethics approval

This is a brief report summarizing patient's clinical course. The Children's Hospital of Michigan Research Ethics Committee has confirmed that no ethical approval is required.

Consent to publish

The authors affirm that parents of our reported patient provided informed consent for publication.

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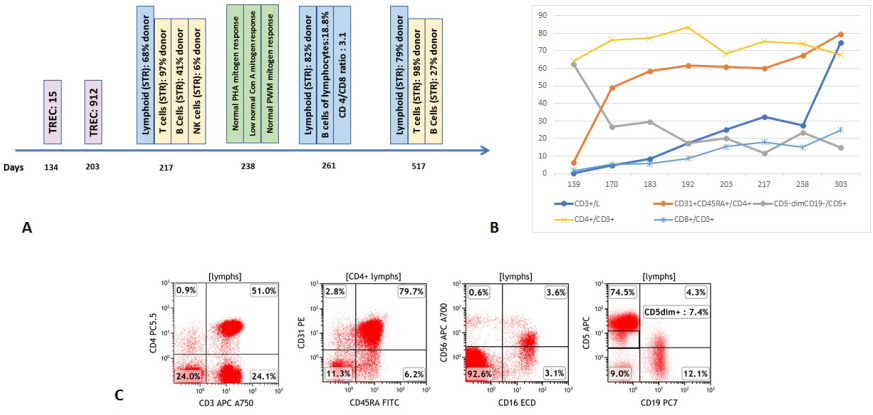
Figure Legend

Figure 1. Immune reconstitution following umbilical cord blood transplantation (UCBT). **A** . Time frame of immune recovery is depicted in this illustration. TREC (T cell receptor excision circles) presented in cells/mcL; STR (short tandem repeat) in percent values; PHA (Phytohemagglutinin); PWM (Pokeweed); Con A (Concanavalin A).**B** . Post-UCBT immune reconstitution course of T cells (CD3+), recent thymic emigrants (RTE) that are CD3+CD4+CD45RA+CD31+, CD5-dim T cells, CD4+ T cells and CD8+ T cells in percent values of the denominator population. Higher CD5-dim T cell ratios in earlier days of immune reconstitution may reflect greater release of maturing thymocytes into circulation. **C** . Flow cytometry histograms reflecting the pattern of CD3+/CD4+ cells, RTE, CD56+/CD16+/– cells and CD5-dim T cells (all gated on lymphocyte population) 10 months following UCBT.



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