Autologous Umbilical Cord Blood Transfusion in Young Children With Type 1 Diabetes Fails to Preserve C-Peptide

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OBJECTIVE—We conducted an open-label, phase 1 study using autologous umbilical cord blood (UCB) infusion to ameliorate type 1 diabetes (T1D). Having previously reported on the first 15 patients reaching 1 year of follow-up, herein we report on the complete cohort after 2 years of follow-up.

RESEARCH DESIGN AND METHODS—A total of 24 T1D patients (median age 5.1 years) received a single intravenous infusion of autologous UCB cells and underwent metabolic and immunologic assessments.

RESULTS—No infusion-related adverse events were observed. β-Cell function declined after UCB infusion. Area under the curve C-peptide was 24.3% of baseline 1 year postinfusion (P < 0.001) and 2% of baseline 2 years after infusion (P < 0.001). Flow cytometry revealed increased regulatory T cells (Tregs) (P = 0.04) and naive Tregs (P = 0.001) 6 and 9 months after infusion, respectively.

CONCLUSIONS—Autologous UCB infusion in children with T1D is safe and induces changes in Treg frequency but fails to preserve C-peptide.
Table 1—Baseline and postinfusion characteristics of autologous UCB recipients

|                      | Preinfusion | 3 months | 6 months | 9 months | 1 year | 1.5 years | 2 years | (Preinfusion–to–1 year ratio) – 1 | (Preinfusion–to–2 year ratio) – 1 |
|----------------------|-------------|----------|----------|----------|--------|-----------|---------|----------------------------------|----------------------------------|
| **HbA1c (%)**        | 7.4 (6.5–8.4) | 7.5 (7.1–8.5) | 7.5 (7.1–8.5) | 7.1 (6.7–7.1) | 7.1 (6.7–7.8) | 7.1 (6.6–7.9) | 7.6 (7.2–8.0) | –0.2 (–0.6 to 0.7) | 0.1 (–0.5 to 0.9) |
| **Insulin use (units/kg per day)** | 0.37 (0.22–0.51) | 0.46 (0.28–0.58) | 0.58 (0.44–0.79) | 0.58 (0.44–0.79) | 0.69 (0.55–0.81) | 0.63 (0.57–0.77) | 0.66 (0.61–0.81) | –0.22 (–0.53 to –0.085) | –0.44 (–0.68 to –0.21) |
| **Peak C-peptide (ng/mL)** | 1.16 (0.7–1.71) | 0.83 (0.24–1.28) | 0.73 (0.47–1.35) | 0.6 (0.08–1.36) | 0.28 (0.16–0.86) | 0.17 (0–0.95) | 0.05 (0–0.58) | –0.53 (–1.0 to –0.16) | –0.7 (–1.4 to –0.5) |
| **AUC C-peptide (ng/mL)** | 0.95 (0.51–1.4) | 0.66 (0.2–1.1) | 0.64 (0.03–1.1) | 0.46 (0.02–0.63) | 0.22 (0.07–0.52) | 0.15 (0–0.82) | 0.02 (0–0.62) | –0.49 (–1.0 to –0.37) | –0.6 (–1.3 to –0.37) |
| **IA-2A**            | 11.0 (1.8–23.1) | 7.5 (0.69–20) | 4.5 (0.2–16.3) | 4.1 (0–16.5) | 2.9 (0–14.5) | 2.2 (0–9.9) | 2.3 (0–8.9) | –3.8 (–7.5 to –3.5) | –7.2 (–12.7 to –2.3) |
| **GADA**             | 2.5 (0.7–12.3) | 1.7 (0.3–6.4) | 1.95 (0.2–9.2) | 2.0 (0.5–15.7) | 2.6 (0.3–15.8) | 1.9 (0–4.3) | 1.2 (0–8.9) | –1.6 (–3.6 to 0.6) | –8.4 (–12.8 to 0) |
| **WBC (cell × 10^9/L)** | 5.6 (5.0–7.3) | 5.75 (4.7–7.85) | 6.1 (4.7–6.9) | 5.8 (4.6–6.9) | 5.8 (4.4–6.7) | 5.5 (3.9–7.6) | 5.5 (4.25–7.35) | –0.7 (–0.7 to 0.2) | –1.8 (–0.8 to 0) |
| **CD4-to-CD8 ratio** | 1.89 (1.5–2.4) | 1.89 (1.6–2.2) | 1.96 (1.5–2.2) | 1.97 (1.6–2.2) | 1.97 (1.4–2.2) | 2.15 (1.7–2.4) | 2.15 (1.7–2.4) | –0.28 (–0.28 to 0.24) | 0.15 (–0.2 to 0.4) |
| **Peripheral blood Treg (%)** | 3.1 (0.8–5.4) | 4.1 (1.0–5.5) | 4.4 (2.0–7.5) | 3.6 (1.9–5.1) | 3.6 (2.0–7.6) | 3.0 (1.8–5.1) | 3.3 (1.9–6.5) | 0.13 (–1.3 to 1.0) | 0.52 (–1.8 to 2.9) |
| **CD45RA Treg (%)**  | 39.0 (25.7–45.9) | 42.6 (27.8–49.8) | 40.5 (34.1–51.3) | 43.5 (37.9–54.3) | 40.9 (31.9–50.4) | 40.2 (29.9–46.2) | 42.8 (28.6–48.8) | –5.53 (–11.0 to 11.1) | 1.82 (–3.8 to 1.8) |

Data are median (interquartile range) and [n] [P value vs. baseline]. N = 24 (10 males, 14 females), median age at infusion 5.1 years (3.4–6.9). IA-2A, insulinoma-associated 2 antibody; GADA, GAD antibody; WBC, white blood cell count.
CONCLUSIONS

A single infusion of minimally manipulated autologous UCB in young children with T1D is feasible and safe but fails to preserve C-peptide. Lack of control subjects (in this case, attributable to internal review board and U.S. Food and Drug Administration restrictions) makes it difficult to form definitive conclusions regarding efficacy. The observation that total Treg frequency was increased up to 6 months after infusion suggests that autologous UCB infusion may favorably alter the T-cell repertoire in children with T1D.

The reasons for an inability of autologous UCB to effectively halt autoimmune progression are at least twofold. First, an insufficient number of cells carrying regenerative or immunoregulatory capacity may have been transferred to patients with T1D. In addition, the ongoing autoimmune response in new-onset T1D subjects may contain memory T cells, refractive to regulation by Tregs (6), that facilitate the ongoing autoimmune destruction of endogenous or de novo β-cells.

To address the first issue, efforts are underway to isolate and expand specific cell populations within UCB to augment their therapeutic potential. As proof of concept, a phase I clinical trial is currently under way in adult patients with recent-onset T1D using autologous expanded Tregs isolated from peripheral blood (clinical trial reg. no. NCT01210664). In terms of the second limitation, studies from our laboratory suggest that a combination therapeutic approach involving transient immune depletion and subsequent induction of immune regulation is optimal (7). As such, we believe that therapies combining transient immune depletion and subsequent infusion of expanded UCB Tregs may more effectively reset the balance of Tregs and effector T cells in T1D.

Although this effort failed to demonstrate benefit, the potential of UCB to participate in future T1D interventional therapies remains. Efforts to use autologous UCB in the treatment of T1D will continue with emphasis on improved understanding of UCB Treg function, the addition of generally regarded as safe therapies (i.e., vitamin D and n-3 fatty acids) to UCB infusion (clinical trial reg. no. NCT00873925), and perhaps most important, the potential use of expanded autologous UCB Tregs either alone or in combination with other immunomodulatory agents.

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