Clinical and immunologic status of a child conceived following maternal administration of CD19 CAR T-cells for systemic lupus erythematosus

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ABSTRACT

Objective. *To report pregnancy outcome and neonatal immune parameters following early conception after maternal CD19 chimeric antigen receptor T-cell (CAR-T) therapy for refractory systemic lupus erythematosus (SLE).*

Methods. *Maternal and neonatal CAR-T cells were assessed by transgene polymerase chain reaction (PCR) at delivery. CD19+ B-cell counts and immunoglobulin levels were measured in maternal and neonatal blood at birth. Infant health outcomes were assessed during the first year of life.*

Results. *Conception occurred approximately seven weeks after CD19 CAR-T infusion. CAR-T cells were not detected in maternal peripheral blood or cord blood at delivery. Neonatal CD19+ B-cell counts and IgG levels were within age-appropriate reference ranges and exceeded maternal values, which remained subnormal. During one year of follow-up, the infant experienced no recurrent or severe infections.*

Conclusion. *This case represents the earliest reported pregnancy following CD19 CAR-T therapy for SLE and the first to include neonatal immune assessment at birth. No evidence of transplacental CAR-T transfer or clinically significant neonatal immunodeficiency was observed. Additional cases and long-term follow-up are required to guide reproductive counseling after CAR-T therapy.*

Introduction

CD19-directed chimeric antigen receptor T (CAR-T) cells selectively target B cells and plasmablasts expressing CD19. This therapy is now established for relapsed or refractory B-cell malignancies and is under active investigation for autoimmune diseases such as systemic lupus erythematosus (SLE), in which B cells play a central pathogenic role. Long-term persistence of CD19 CAR-T cells, lasting months to years after infusion, has been well documented in patients with haematologic malignancies (1). In this population, CAR-T therapy frequently results in prolonged B-cell aplasia that may persist even after CAR-T cells are no longer detectable by flow cytometry or quantitative polymerase chain reaction (PCR) (2). In contrast, in most patients with autoimmune diseases such as SLE CAR-T cells are detectable for as little as 2–3 weeks to up to 3–6 months post-infusion, and B cells become reconstituted after an average time of 110 days (3).

These observations raise theoretical concerns regarding pregnancy following CAR-T therapy for autoimmune diseases. Maternal T cells are known to cross the placenta, persist long-term in the offspring, and remain functionally active. In murine models, pathogen-specific maternal T cells transferred during pregnancy persist into adulthood and may provide immune protection (4). In humans, maternal T cells reside in foetal lymphoid tissues and promote tolerance by inducing regulatory T cells, with persistence reported into early adulthood (5). If maternal CD19 CAR-T cells were similarly transferred and remained functional in the foetus, they could suppress developing B-cell populations and potentially lead to prolonged immunodeficiency requiring immunoglobulin replacement therapy.

Data regarding pregnancy outcomes following CAR-T therapy remain extremely limited, particularly in autoimmune disease. We report a case of early conception following CD19 CAR-T therapy for refractory SLE, with detailed immunologic evaluation of both mother and infant at delivery.

Case report

A 30-year-old Hispanic woman with SLE diagnosed at age 13 presented with a history of fever, inflammatory polyarthritis, photosensitive malar rash, immune thrombocytopenic purpura, Coombs-positive haemolytic anaemia, and class IV/V lupus nephritis. Serologic features included high-titre anti-double-stranded DNA, anti-Smith, anti-RNP, and anti-SSA antibodies, lupus anticoagulant, and persistent hypocomplementaemia.

Prior therapies included hydroxychloroquine, variable-dose prednisone, azathioprine (2014–2018), and rituximab (2018–2022). In June 2022, while off prednisone, she experienced a severe disease flare with malar rash, headache,

Table I. Maternal and neonatal immunologic parameters at birth.

Parameter	Mother	Newborn
$CD19^+$ B cells (cells/μL)	74 (81–409)	242 (120–2324)
IgG (mg/dL)	282 (700–1600)	530 (496–1231)
IgM (mg/dL)	82 (40–230)	15 (3–10)
IgA (mg/dL)	55 (70–400)	<5 (2–362)

Values in parentheses indicate reference ranges for adults (mother) and neonates.

Table II. Reported pregnancies following CAR T-cell therapy.

Reference	Disease	Conception	Neonatal immune status
Ligon (6)	Lymphoma (4 cases)	>1 year	Not reported
Canty (7)	Lymphoma	5 years	Normal B cells and IgG
O'Reilly (8)	Lymphoma	10 months	Transient ↓ B cells and IgG
O'Reilly (8)	Lymphoma	34 months	Normal B cells and IgG
Jiang (9)	SLE	6, 21 months	Normal B cells and IgG*
Our case	SLE	7 weeks	Normal B cells and IgG

*measured 1 year and 3 months after birth.

oral ulcers, and new-onset nephrotic-range proteinuria. Laboratory evaluation revealed a serum creatinine of 1.9 mg/dL, and 24-hour urine protein excretion of 10 g. Renal biopsy demonstrated class IV/V lupus nephritis with mild-to-moderate interstitial fibrosis, active interstitial nephritis, 11 cellular crescents, and no evidence of thrombotic microangiopathy.

She was treated with pulse methylprednisolone followed by oral prednisone (0.5 mg/kg daily) and mycophenolate mofetil, later transitioned to mycophenolic acid due to intolerance. Belimumab was added without clinical improvement, followed by voclosporin in July 2023. Despite combination therapy, she developed chronic kidney disease with serum creatinine of 1.34 mg/dL, had persistent proteinuria (urine protein-to-creatinine ratio [UPCR] 3.0 mg/mg), hypocomplementaemia (C3 63 mg/dL, C4 5 mg/dL), inflammatory arthralgias, and daily headaches.

In September 2023, she enrolled in a clinical trial of CC-97540 (BMS-986353), an investigational CD19 CAR-T therapy for refractory SLE. After withdrawal of immunosuppressive medications, she underwent lymphodepletion with cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2) for three days, followed by CAR-T infusion on November 16, 2023. She achieved rapid serologic and clinical remission, including resolution of extra-renal manifestations, without resumption of hydroxychloroquine or immunosuppressive therapy.

Peripheral blood $CD19^+$ B cells were undetectable in December 2023 and remained markedly suppressed in January 2024. CAR-T cells became undetectable by transgene PCR on January 12, 2024, 57 days post-infusion. The patient conceived in early January 2024, 7 weeks after CAR-T infusion. Pregnancy was confirmed in February 2024.

Institutional review board approval and informed consent were obtained to assess maternal and neonatal immune parameters. The pregnancy was complicated by pre-eclampsia requiring therapy of hypertension with labetalol, with serum creatinine peaking at 2.10 mg/dL and UPCR rising to 12.14 mg/mg. She underwent induction of labour at 37 weeks' gestation, delivering a healthy male infant (Apgar score 9) weighing 4 lb. 8 oz.

At delivery, CAR-T cells were undetectable by transgene PCR in maternal peripheral blood and cord blood. CD19+ B-cell counts, and immunoglobulin levels obtained one day postpartum are shown in Table I. The infant, who was breastfed, has remained healthy through one year of follow-up, with the exception of a mild influenza infection at eight months of age and no history of recurrent or severe infections.

The mother's repeat renal biopsy two months postpartum showed resolution of prior proliferative lesions, with residual membranous changes, interstitial fibrosis, and sclerosis of 20 of 37 glomeruli. She was placed back on hydroxychloroquine with addition of tacrolimus at that time. At one year postpartum, serum creatinine was 1.17 mg/dL and UPCR was 0.92 mg/mg. Her SLE remains clinically and serologically inactive.

Discussion

Pregnancy outcomes following CAR-T therapy are poorly characterised, with limited published data largely confined to patients treated for haematologic malignancies (Table II). Ligon *et al*. reported four successful pregnancies following CAR-T therapy, all conceived at least one year after infusion; however, neonatal immune outcomes were not described (6).

To date, there has been no confirmed documentation of transplacental CAR-T cell transfer. Canty *et al*. reported a woman who conceived five years after CAR-T infusion. CAR-T cells were detectable in maternal blood and breast milk, but absent in the infant, who had normal B- and T-cell subsets and immunoglobulin levels at birth (7). Similarly, O'Reilly *et al*. described two pregnancies conceived 10 and 34 months after CAR-T therapy. One infant had transient B-cell lymphopenia and hypogammaglobulinaemia that resolved within six months, while the second infant had normal immune parameters. (8).

Jiang *et al*. recently reported an SLE patient who conceived pregnancies 6-months and 21-months after receiving therapy with CD19/BCMA CAR-T cells for refractory lupus nephritis. CAR-T cells were detected in the mother's blood at 7 months and not detected at 16 months after CAR-T infusion. CAR-T cells were not detected in the blood of either baby 48 hours after birth and both babies had normal immunoglobulins and lymphocyte subsets, the first at 1 year and the second at 3 months (9).

The present case represents the earliest reported conception following CAR-T therapy, occurring approximately seven weeks after infusion, and is the first to include detailed neonatal immune as-

sessment in SLE. Although CAR-T cells were undetectable shortly before conception, the mother remained profoundly B-cell depleted, raising concerns that CAR-T cells might still be present but below the level of PCR assay detection, therefore still posing a threat for potential foetal immune effects. Reassuringly, the infant demonstrated higher $CD19^+$ B-cell counts and IgG levels than the mother at birth, with normal clinical immune function during the first year of life.

Long-term risks associated with CAR-T therapy include secondary malignancies and T-cell lymphomas related to genetic modification, raising theoretical concerns regarding transgenerational risk (10). Continued longitudinal follow-up of this child and systematic reporting of additional pregnancies following CAR-T therapy will be essential to inform future reproductive counselling and clinical guidelines.

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