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Pregnancy and Infant Outcomes Post–CD19-Directed CAR-T Therapy: Tisagenlecleucel and/or huCAR19 (CTL119)

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KEY MESSAGES AND CONCLUSION

- This retrospective cohort analysis demonstrates that pregnancy and the delivery of healthy infants are possible following CD19-directed CAR-T therapy, such as tisagenlecleucel or CTL119
- Utilizing CAR-T therapy earlier in the patient management journey may enhance the chances of healthy pregnancy by mitigating the infertility risks associated with cumulative and/or high-dose chemotherapy and radiation, especially when used as conditioning regimens for HSCT
- Despite the theoretical risk of cross-placental transmission of CAR-T cells, the data suggest that, with appropriate maternal care healthy infant outcomes can be achieved
- It is important to consider long-term follow-up of the infant through at least the first year of life, with close attention to growth and development. Monitoring the mother for BCA/ongoing IVIG supports testing the infant's B-cell level at birth and considering transgene testing if the infant has a low B-cell level
- Continued collection and reporting of pregnancy outcomes after CAR-T therapy remain crucial to further understand and optimize fertility preservation and maternal–infant health in this patient population
- Testing infant B cells at birth should be considered in cases where maternal BCA and/or ongoing IVIG therapy is involved
- This is a largest cohort reporting pregnancy and infant outcomes after CD19 CAR-T infusion across ALL, DLBCL and FL indications

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INTRODUCTION

- Chimeric antigen receptor T-cell (CAR-T) therapy has revolutionized cancer treatment and improved clinical outcomes across relapsed or refractory (r/r) hematological B-cell malignancies[1]
- Despite these advancements, the impact of CAR-T therapy on pregnancy and infant outcomes remains largely unexplored[2]
- There is significant variability in peri-CAR-T cell fertility guidance and fertility preservation practices. Most centers lack established guidelines for fertility preservation or long-term fertility outcomes, and the impact of CAR-T cells on a developing fetus remains unclear[2]
- Recent real-world evidence (RWE) for pediatric-young adult B-cell acute lymphoblastic leukemia[3] (B-ALL) and NCCN clinical practice guidelines in oncology[4] support the use of tisagenlecleucel for r/r B-ALL
- Recent RWE from CIBMTR[5,6] and updated results from the pivotal JULIET trial[7] and ELARA trial[8] support the use of tisagenlecleucel for r/r B-cell non-Hodgkin's lymphoma (B-NHL)
- There is a theoretical risk of cross-placental transmission of CAR-T cells in female patients during pregnancy. The impact of CAR-T therapy on fertility, conception, or pregnancy in both male and female patients is uncertain[9,10]
- High-dose or cumulative high-dose chemotherapy and/or radiation, especially regimens associated with haematopoietic stem cell transplantation (HSCT), has a high infertility risk. Use of CAR-T therapy earlier in the patient management journey may increase the chance of fertility preservation[2]
- In this study, we analyzed and reported the pregnancy outcomes of patients treated with tisagenlecleucel (CTL019, muCAR19) or CTL119 (humanized CAR-T [huCAR19])

METHODS

- In this retrospective cohort analysis, a cumulative search in the Novartis Global Safety database for all CAR-T products, up to April 16, 2025 was conducted using the Standard MedDRA Query: Pregnancy and neonatal topics (narrow)
- CAR transgene levels were monitored in clinical trial patients for all indications. Ongoing B-cell aplasia (BCA)/deficiency or intravenous immunoglobulin (IVIG) treatment was used as a surrogate marker for persistence of CAR-T cells in patients treated with commercial tisagenlecleucel with B-ALL
- Pregnancy outcomes were collected via pregnancy and infant forms at birth,3 months, and 12 months, subject to reporter and/or patient's consent
- Remission/relapse status for patients with B-ALL and response status for patients with diffuse large B-cell lymphoma or follicular lymphoma were captured when feasible

RESULTS

- Seventeen events of tisagenlecleucel or CTL119 exposure during pregnancy were reported. Elective termination of pregnancy was noted in 3 cases. Pathology review of placental/fetal parts in 1 of these cases was unremarkable. One case each did not have consent for follow-up and newborn status. The remaining twelve pregnancies resulted in the live birth of 13 healthy infants (1 pregnancy with twins). Further details of these 12 pregnancies are provided in **Table 1**.

Table 1. Details about reported pregnancies

Patient number	Indication	Product received	Gender of the patient	Approximate age of patients at conception	Approximate time from CAR-T to conception	Latest follow-up of healthy infant(s)
1*	B-ALL	Tisagenlecleucel	Female	22 years	1 year	2 years
2*	B-ALL	Tisagenlecleucel	Male	25 years	3 years	8 months
3*	B-ALL	Tisagenlecleucel	Female	19 years	2 years 6 months	3 weeks
4	3L B-ALL	CTL119	Female	20 years	3 years	22 months
5	3L B-ALL	CTL119	Male	30 years	6 years 6 months	18 months
6	3L B-ALL	CTL119	Female	29 years	8 years	Birth
7	3L B-ALL	CTL019#	Male	39 years	1 year 6 months	12 months
8	1L B-ALL	CTL019#	Male	25 years	7 months	21 months
9	3L B-ALL	CTL019#	Male	35 years	2 years 6 months	Birth (twins)
10	3L B-ALL	CTL019#	Female	28 years	6 years 9 months	Birth
11	2L B-NHL	CTL019#	Female	31 years	1 year 7 months	Birth
12	3L FL	CTL019#	Male	33 years	1 year 3 months	12 months

*Commercial tisagenlecleucel; #Tisagenlecleucel used in clinical trial is defined as CTL019

1L, first line; 2L, second line; 3L, third line; B-ALL, B-cell acute lymphoblastic leukemia; B-NHL, B-cell non-Hodgkin's lymphoma; CAR-T, chimeric antigen receptor T cell; FL, follicular lymphoma.

- CAR transgene (muCAR19 or huCAR19) levels were available for clinical trial patients (**Table 2**). Persistent CAR transgene levels in clinical trial patients with B-ALL have shown concordance with the use of IVIG/ongoing BCA/deficiency (data not shown)
- Among 9 clinical trial patients, 2 had ongoing IVIG during pregnancy and 3 at the time of delivery, whereas among 3 commercial tisagenlecleucel patients, 2 had ongoing IVIG during pregnancy and 1 at the time of delivery (**Table 2**)

Table 2. Details about IVIG, transgene data, and B-cell data

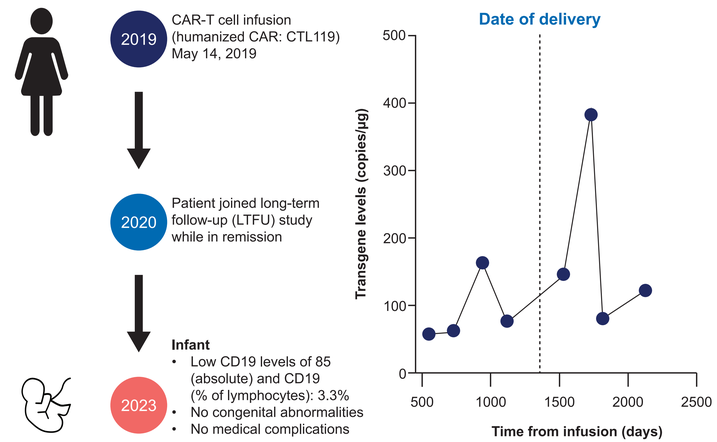
Patient number	Indication	Product received	Gender of the patient	IVIG used at pregnancy	IVIG used at delivery	Transgene data results at delivery	B-cell data available at delivery
1*	B-ALL	Tisagenlecleucel	Female	Yes	Yes	No	Yes BCA
2*	B-ALL	Tisagenlecleucel	Male	Yes	Not applicable	No	Yes BCA
3*	B-ALL	Tisagenlecleucel	Female	Yes	Yes	No	Yes BCA
4	3L B-ALL	CTL119	Female	Yes	Yes	Yes	Yes BCA
5	3L B-ALL	CTL119	Male	Yes	Not applicable	Yes	Yes
6	3L B-ALL	CTL119	Female	Data not available	Yes	Yes	Yes
7	3L B-ALL	CTL019#	Male	No	No	Yes	Yes
8	1L B-ALL	CTL019#	Male	No	No	Yes	Yes
9	3L B-ALL	CTL019#	Male	No	No	Yes	Yes
10	3L B-ALL	CTL019#	Female	No	Yes	Yes	Yes
11	2L B-NHL	CTL019#	Female	No	No	Yes	Yes
12	3L FL	CTL019#	Male	No	Not applicable	Yes	Yes

*Commercial tisagenlecleucel; #Tisagenlecleucel used in clinical trial is defined as CTL019

1L, first line; 2L, second line; 3L, third line; B-ALL, B-cell acute lymphoblastic leukemia; BCA, B-cell aplasia; B-NHL, B-cell non-Hodgkin's lymphoma; CAR-T, chimeric antigen receptor T cell; FL, follicular lymphoma; IVIG, intravenous immunoglobulin.

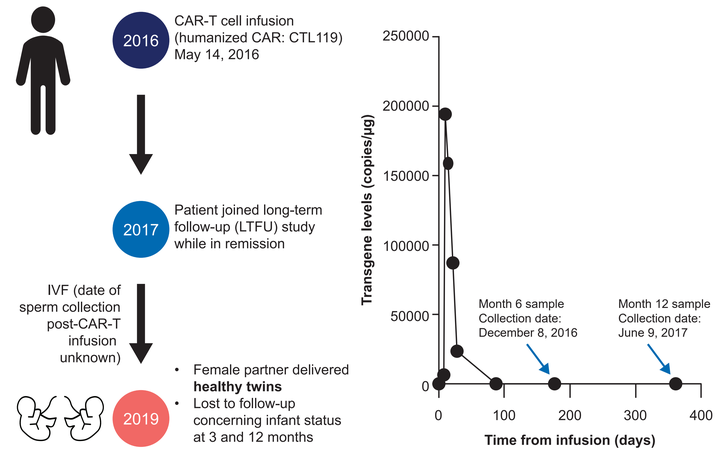
- Four cases were particularly informative. The mother of 1 child was enrolled in the long-term follow-up study, had BCA for approximately 3 years after CTL119, and tested positive for persistent CAR by quantitative polymerized chain reaction. Both tests indicated circulating CAR during pregnancy. The child tested negative for huCAR19 transgene on day 7 of life, although the number of B cells (80 cells/μL) was notably low at birth. Immunoglobulin G levels in the child and the mother were normal because of appropriate maternal IVIG supplementation. The low B-cell count, which then normalized, suggested the possibility of cross-placental transmission of CAR-T cells, producing transient in utero B-cell hypoplasia, which resulted in the child's immune system rejecting CAR-T (**Figure 1**).
- Two of the commercial tisagenlecleucel female patients had BCA and ongoing IVIG at the time of delivery. B cells were checked on these infants and was 629 cells/μL for infant of patient number 3. CAR transgene from cord blood is pending on the infant of patient 1 and 3.
- One of the male patients treated during the pivotal study for 3L FL had conception by IVF, and the female partner delivered a healthy infant with update at 1 year of age (**Figure 2**)

Figure 1. Journey of a patient number 4



- Infant had blood tested at the day 7 of life and transgene was not detected.

Figure 2. Journey of a patient number 12



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