# Recurrent Urinary Tract Infections and Low Secretory IgA Following CD19-directed CAR T Cell Therapy for Relapsed Acute Lymphoblastic Leukemia

Isaac Bettina McGraw, MD[1], Colleen Sweeney, NP[2], Süreyya Savaşan, MD[1-2]

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Carmen and Ann Adams Department of Pediatrics,

[1]Division of Hematology/Oncology

[2]Blood and Marrow Transplant Program

Children's Hospital of Michigan,

Barbara Ann Karmanos Cancer Center,

Wayne State University School of Medicine, Detroit, MI

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/pbc.26739.

Correspondence: Süreyya Savaşan, MD

Division of Hematology/Oncology

Pediatric Blood and Marrow Transplantation Program

Children's Hospital of Michigan

Barbara Ann Karmanos Cancer Center

Wayne State University School of Medicine

ssavasan@med.wayne.edu

313-745-5515 (Phone)

313-745-5237 (Fax)

Running title: Recurrent UTI following CD19-directed CAR T Cell Therapy

Word Count: 525

**List of Abbreviations:**

| | |
|---|---|
| CD | Cluster of Differentiation |
| CART | Chimeric Antigen Receptor |
| E. coli | Escherichia coli |
| Ig | Immunoglobulin |
| TCT | T-cell therapy |
| UK-ALL R3 | United Kingdom protocol for refractory and relapsed Acute Lymphoblastic Leukemia |

To the Editor:

CD19-directed CAR T cell therapy (CD19-CAR-TCT) has been successful as a novel modality in treating recurrent or refractory B-lineage acute lymphoblastic leukemia (B-ALL) (1-2). Despite absence of circulating B lymphocytes, severe pan-hypogammagobulinemia, decreased plasma cell (PC) content and B cell aplasia in tissues, persistence of some humoral immune response mediated by remaining CD19-negative PC was shown following CD19-CAR-TCT (3). The authors further emphasized the need for investigating mucosal antibodies in these patients. Our case constitutes an example of potential CD19-CAR-TCT complication due to impaired secretory immune response.

A, currently, 10-year-old female with standard-risk B-ALL started treatment before relocating to the United States in 2011. She also has history of vitamin B12 deficiency from infancy, which later was discovered to be due to hereditary intrinsic factor deficiency (4-5). She continued treatment, but experienced systemic relapse 22 months from diagnosis while receiving maintenance chemotherapy. She was then treated per the UK ALL-R3 regimen, but did not achieve complete remission. She underwent matched sibling bone marrow transplantation (BMT) relapsing in the bone marrow 5 months after BMT. Following clofarabine and cytarabine chemotherapy, she developed secondary hemophagocytic lymphohistiocytosis with multi-organ failure. However, she achieved and had remained in complete remission for 10 months. Due to systemic relapse, she underwent CD19-CAR-TCT at another institution 28 months ago. She has been supplemented with intravenous immunoglobulin regularly and continues to be in remission with undetectable peripheral blood B lymphocytes and serum IgA and IgM levels.

Prior to CD19-CAR-TCT, the patient had 3 separate urinary tract infections (UTI) secondary to E. coli during 40 months of follow up, which clustered in less than a 3-month period and corresponded to the time of BMT when she was on graft-versus-host disease prophylaxis. Both immune suppression and possible incomplete eradication supported by the observation of short intervals between UTI episodes might have contributed to recurrence. She had 3 UTI episodes 14, 18 and 23 months after CD19-CAR-TCT due to E. coli and P. mirabilis with negative renal/bladder ultrasound and voiding cystourethrography studies. Salivary secretory IgA (sIgA) levels were very low on two measurements at 0.31 and 0.35, respectively (normal: 5-28).

Secretory IgA predominates the immunoglobulin content in secretions and is produced by local stromal or nodal tissue PC along with joining (J) chain, which binds two or more IgA monomers that associates with an epithelial glycoprotein called 'secretory component' facilitating secretion to mucosal surfaces. Monomeric IgA can be also found in mucosal secretions, making 13-17% of the salivary IgA and 77% of the salivary monomeric IgA that is estimated to be serum-derived (6). Secretory IgA is critical in mucosal pathogenic microorganism colonization by preventing bacterial adherence, agglutinating microorganisms, interfering with bacterial motility and neutralizing bacterial enzymes and toxins (7). Furthermore, binding of sIgA by E. coli protein was shown to inhibit neutrophil activation (8).

Low urinary tract sIgA has been linked to recurrent symptomatic bacteriuria in females with normal urinary tracts (9). While salivary sIgA does not directly reflect urine sIgA status, it may suggest possible low sIgA level in the urine. Thus, low salivary sIgA should warrant testing sIgA levels in the urine given the nature of humoral immunodeficiency associated with CD19-CAR-TCT in such cases.

**References**

1. Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, Teachey DT, Chew A, Hauck B, Wright JF, Milone MC, Levine BL, June CH. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med. 2013;368:1509-18.
2. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, Chew A, Gonzalez VE, Zheng Z, Lacey SF, Mahnke YD, Melenhorst JJ, Rheingold SR, Shen A, Teachey DT, Levine BL, June CH, Porter DL, Grupp SA. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371:1507-17.
3. Bhoj VG, Arhontoulis D, Wertheim G, Capobianchi J, Callahan CA, Ellebrecht CT, Obstfeld AE, Lacey SF, Melenhorst JJ, Nazimuddin F, Hwang WT, Maude SL, Wasik MA, Bagg A, Schuster S, Feldman MD, Porter DL, Grupp SA, June CH, Milone MC. Persistence of long-lived plasma cells and humoral immunity in individuals responding to CD19-directed CAR T-cell therapy. Blood. 2016;128:360-70.
4. Zia A, Fışgin T, Sokolowski C, Tanner SM, Savaşan S. Acute lymphoblastic leukemia and vitamin B12 deficiency secondary to a gastric intrinsic factor gene mutation. Pediatr Blood Cancer. 2012;59:766-7.
5. Sturm AC, Baack EC, Armstrong MB, Schiff D, Zia A, Savasan S, de la Chapelle A, Tanner SM. Hereditary intrinsic factor deficiency in chaldeans. JIMD Rep. 2013;7:13-8.
6. Brandtzaeg P. Do salivary antibodies reliably reflect both mucosal and systemic immunity? Ann N Y Acad Sci. 2007;1098:288-311.
7. van Egmond M, Damen CA, van Spriel AB, Vidarsson G, van Garderen E, van de Winkel JG. IgA and the IgA Fc receptor. Trends Immunol. 2001;22:205-11.
8. Pastorello I, Rossi Paccani S, Rosini R, Mattera R, Ferrer Navarro M, Urosev D, Nesta B, Lo Surdo P, Del Vecchio M, Rippa V, Bertoldi I, Gomes Moriel D, Laarman AJ, van Strijp JA, Daura X, Pizza M, Serino L, Soriani M. EsiB, a novel pathogenic Escherichia coli secretory immunoglobulin A-binding protein impairing neutrophil activation. MBio. 2013 Jul 23;4(4).
9. Fliedner M, Mehls O, Rauterberg EW, Ritz E. Urinary sIgA in children with urinary tract infection. J Pediatr. 1986;109:416-21.