RETHYMIC®
allogeneic processed thymus tissue-agdc

James | a 4-year-old male diagnosed with congenital athymia

▶ Presentation and diagnosis

- **T cell receptor excision circle (TREC) newborn screening** detected a deficiency of naive T cells, which may indicate either severe combined immunodeficiency (SCID) or congenital athymia[1]
- Underwent **complete blood count differential and lymphocyte phenotyping** by flow cytometry. Fewer than 50 naive T cells/mm^3 were detected in the peripheral blood. The patient presented with a $T^-B^+NK^+$ phenotype, indicating a need for further testing[1]
- Additional **panel-based genetic testing** ruled out SCID[1]
- Chromosomal microarray identified 22q11.2 deletion, **confirming a congenital athymia diagnosis** associated with complete DiGeorge syndrome[1]

This is a hypothetical patient case study and is not indicative of treatment outcomes.

The steps to confirming a diagnosis presented here are not exhaustive and may differ on a case-by-case basis.

Additional supportive care may be needed to manage a patient's associated conditions. These may include complete DiGeorge syndrome (22q11.2 deletion syndrome), CHARGE* syndrome, *FOXN1* deficiency, and diabetic embryopathy.[1]

▶ Supportive care plan

- **Infection control measures were initiated** in the hospital immediately following the positive TREC screening results and suspicion of congenital athymia[1]
  - **Isolation:** The patient was placed in a room with laminar air flow (LAF). Visitors were required to properly sterilize and wear personal protective equipment (PPE) before entering[1]
  - **Supportive therapies:** Started on prophylaxis for *Pneumocystis jirovecii*; immunoglobulin (IgG) replacement therapy; and antibiotic, antimicrobial, and antifungal prophylaxis[1,2]
  - Received no live or inactive vaccines[3]
  - Mother was instructed to stop breastfeeding to decrease risk of cytomegalovirus (CMV) transmission[1]
- **After confirmation of congenital athymia and the patient was deemed appropriate for treatment, the patient was referred to a qualified treatment center** to receive RETHYMIC[4]
  - **Discharged from the hospital** and brought home until treatment with RETHYMIC became available
  - It was recommended that this family follow strict isolation measures, including restricting visitors and frequent handwashing[3]

*Coloboma, heart defects, atresia of the nasal choanae, retardation of growth and development, genitourinary anomalies, and ear anomalies.

Indication

RETHYMIC® is indicated for immune reconstitution in pediatric patients with congenital athymia.

Limitations of Use: RETHYMIC is not indicated for the treatment of patients with severe combined immunodeficiency (SCID).

Important Safety Information

Infection Control and Immunoprophylaxis: Immune reconstitution sufficient to protect from infection is unlikely to develop prior to 6-12 months after treatment with RETHYMIC. Follow infection control measures until the development of thymic function is established as measured by flow cytometry. Closely monitor patients for signs of infection. If fever develops, assess the patient via lab results and treat as clinically indicated. Patients should be maintained on immunoglobulin replacement therapy (IgG) and *Pneumocystis jirovecii* pneumonia prophylaxis until specified criteria are met. IgG trough level should be checked 2 months after stopping IgG to determine whether the patient may remain off IgG.

Please see additional Important Safety Information throughout, and full Prescribing Information.

James' congenital athymia treatment journey

This is a hypothetical patient case study and is not indicative of treatment outcomes or timing. Exact timelines may vary from patient to patient. Please see full Prescribing Information for guidance on testing and monitoring parameters.

Birth | **1 Week** | **2 Weeks** | **2 Years** | ***The journey continues***

1 Week: Positive TREC screening results

At suspicion of congenital athymia[1]:

- Infection control measures were initiated

2 Weeks: James' congenital athymia diagnosis was confirmed

After diagnosis was confirmed[4]:

- Referred for treatment with RETHYMIC

Maintained on supportive care until James was selected for treatment with RETHYMIC[4]

Prior to receiving treatment with RETHYMIC[4]:

- Tested for Epstein-Barr virus (EVB), CMV infection, and renal impairment to assess the risks and benefits of receiving treatment with RETHYMIC
- Thyroid function studies were performed to monitor for autoimmune disorders
- Screens for anti-HLA antibodies were negative
- HLA matching was not required as the patient had not received a prior hematopoietic cell transplantation (HCT) or solid organ transplant

2 Years: James received treatment with RETHYMIC at a qualified treatment center[4]

After returning to the care of his referring healthcare provider[3-5]:

- Monitored closely for signs of infection, including fever. If a fever were to develop, protocols included assessing the patient by blood and other cultures and treating with antimicrobials as clinically indicated
- Naive T-cell counts were monitored using flow cytometry every 3 months until naive T cells were greater than 10% of total T cells
- Monitored for autologous graft versus host disease (GVHD) and autoimmune disorders. Tests for monitoring autoimmune disorders included or measured:
  - Complete blood count with differential (weekly in the first 2 months after treatment)
  - Liver enzymes, serum creatinine levels, and urinalysis (monthly for 3 months after treatment)

Important Safety Information (cont'd)

Graft versus Host Disease (GVHD): RETHYMIC may cause or exacerbate pre-existing GVHD, for which patients should be closely monitored and treated. Risk factors include atypical complete DiGeorge anomaly phenotype, prior hematopoietic cell transplantation (HCT), and maternal engraftment. Patients with specified elevated baseline T cell proliferative response to PHA should receive immunosuppressants to decrease this risk. GVHD may manifest as fever, rash, lymphadenopathy, elevated bilirubin and liver enzymes, enteritis, and/or diarrhea.

Autoimmune Disorders: Autoimmune-related adverse events occurred in patients treated with RETHYMIC. These events included thrombocytopenia, neutropenia, proteinuria, hemolytic anemia, alopecia, hypothyroidism, autoimmune hepatitis, autoimmune arthritis, transverse myelitis, albinism, hyperthyroidism, and ovarian failure. Monitor complete blood counts with differential, liver enzymes, serum creatinine, urinalysis, and thyroid function.

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Continuing to monitor James after treatment with RETHYMIC

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2 Years, 2 Months

2 months after treatment[4]:

- From this point, complete blood count with differential was performed monthly

2 Years, 3 Months

3 months after treatment[3,4]:

- Tested for Epstein-Barr virus (EBV) and CMV infection
- Naive T-cell counts were monitored using flow cytometry
- From this point, liver enzymes and serum creatinine levels were tested and urinalysis was performed every 3 months

2 Years, 6 Months

First evidence of naive $CD4^+$ T cells detected post-implantation[4]

6 months after treatment[3,4]:

- Naive T-cell counts were monitored using flow cytometry
- Thyroid function studies were performed

2 Years, 9 Months

9 months after treatment[3,4]:

- Naive T-cell counts were monitored using flow cytometry

The journey continues

Immune reconstitution sufficient to protect against infection is unlikely to develop prior to 6 to 12 months after treatment with RETHYMIC. For some patients, it may take up to 2 years.[4]

Not an actual patient.

Important Safety Information (cont'd)

Renal Impairment: Pre-existing renal impairment is a risk factor for death.

Cytomegalovirus Infection (CMV): In the clinical studies, 4 out of 4 patients with pre-existing CMV infection died.

Malignancy: Due to underlying immune deficiency, patients who receive RETHYMIC may be at risk of developing post-treatment lymphoproliferative disorder. Patients should be tested for Epstein-Barr virus and CMV prior to and 3 months after treatment or after any suspected exposure.

Transmission of Serious Infections and Transmissible Infectious Diseases: Transmission of infectious disease may occur because RETHYMIC is derived from human tissue, and product manufacturing includes porcine- and bovine-derived reagents.

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Relaxing James' infection prevention measures and administering vaccines

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3 Years

Continued testing to determine if James could discontinue supportive care treatments and therapies[4]

12 months after treatment[3,4]:

- At least 10% of $CD3^+$ T cells were naive in phenotype
- Patient met all requirements and began discontinuing immunosuppression
- Naive T-cell counts were monitored using flow cytometry
- Thyroid function studies were performed
- From this point, monitoring of naive T-cell counts and tests for monitoring autoimmune disorders were performed every 12 months

After discontinuing immunosuppression[4]:

- Phytohemagglutinin (PHA) response was within normal limits
- Patient met all requirements and began discontinuing IgG replacement therapy
- Once the $CD4^+$ cell count was determined to be >200 cells/mm^3 and the patient met all requirements, the patient began discontinuing prophylaxis for *Pneumocystis jirovecii*

3 Years, 3 Months

James received his first inactivated vaccine[4]

2 months after discontinuing IgG replacement therapy[4]:

- IgG trough levels were checked 2 months after discontinuation
- Levels were determined to be in the normal range and the patient remained off IgG replacement therapy

15 months after treatment[4]:

- Total $CD4^+$ T-cell count was >200 cells/mm^3
- $CD4^+$ T cells outnumbered $CD8^+$ T cells
- No more than 2 inactivated vaccines were received per month

After receiving all inactivated vaccines[3]:

- Inactivated vaccines were proven to be effective
- The patient's healthcare provider may consider administering live vaccines

Live virus vaccines should not be administered until the criteria for inactivated vaccines have been met and the patient has received vaccinations with inactivated agents (eg, tetanus toxoid). See all of the requirements for inactivated and live vaccines outlined in the Prescribing Information.[4]

4 Years

James' current age

Learn more about congenital athymia and treatment with RETHYMIC.

Visit RETHYMIC.com/hcp

Important Safety Information (cont'd)

Vaccine Administration: Immunizations should not be given in patients treated with RETHYMIC until immune-function criteria have been met. Live virus vaccines should not be given until patients have met the criteria for and received inactivated vaccines.

Anti-HLA Antibodies: All patients should be screened for anti-HLA antibodies prior to receiving RETHYMIC. Patients testing positive should receive RETHYMIC from a donor who does not express those HLA alleles.

HLA Typing: HLA matching is required in patients who have received a prior HCT or a solid organ transplant. Patients who have received a HCT are at increased risk of developing GVHD after RETHYMIC if the HCT donor does not fully match with RETHYMIC.

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Deaths: Of the 105 patients in clinical studies, 29 patients died, including 23 deaths in the first year (<365 days) after implantation.

Adverse Reactions: The most common (>10%) adverse events included hypertension, cytokine release syndrome, rash, hypomagnesemia, renal impairment/failure, thrombocytopenia, and GVHD.

References: 1. Collins C, Sharpe E, Silber A, Kulke S, Hsieh EWY. Congenital athymia: genetic etiologies, clinical manifestations, diagnosis, and treatment. *J Clin Immunol*. 2021;41(5):881-895. doi:10.1007/s10875-021-01059-7 **2.** Markert ML. Defects in thymic development. In: Sullivan KE, Stiehm ER, eds. *Stiehm's Immune Deficiencies: Inborn Errors of Immunity.* 2nd ed. Elsevier; 2020:357-379. **3.** Gupton SE, McCarthy EA, Markert ML. Care of children with DiGeorge before and after cultured thymus tissue implantation. *J Clin Immunol*. 2021;41(5):896-905. doi:10.1007/s10875-021-01044-0 **4.** RETHYMIC [package insert]. Marlborough, MA: Sumitomo Pharma America, Inc; 2023. **5.** Markert ML, McCarthy EA, Gupton SE, Lim AP. Cultured thymus tissue transplantation. In: Sullivan KE, Stiehm ER, eds. *Stiehm's Immune Deficiencies: Inborn Errors of Immunity*. 2nd ed. Elsevier; 2020:1229-1239.

Please see full Prescribing Information.

ENZYVANT
CONNECT

Education and financial assistance are available through our patient support program, Enzyvant CONNECT®

Enzyvant CONNECT provides patients and their caregivers with personalized support as they navigate the congenital athymia journey.

Enzyvant CONNECT is available to patients with any type of insurance—including commercial plans, Medicare, or Medicaid—as well as patients who are underinsured or have no insurance coverage.

Call 844-ENZCNCT (844-369-2628) to get connected to personalized support. We're available Monday–Friday, 8:00 AM to 8:00 PM ET.

Enroll your patients today

Dedicated care team

- The Support Liaison will help you understand your child's diagnosis
- The Access Specialist can help you navigate insurance benefits and financial assistance

Access to exclusive resources

- Document organizer
- *Sadie's Search*, a storybook written specifically with your child in mind
- Interactive T-cell progress tracker
- Activity book
- And more!

Co-pay program

- The Enzyvant CONNECT® Commercial Co-Pay Program can help caregivers of eligible commercially insured patients in the US and US territories
- You may receive co-pay assistance for medication-related out-of-pocket costs for RETHYMIC

Sumitomo Pharma America, Inc. and Enzyvant CONNECT are not responsible for treatment decisions or timing for treatment.

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