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Medical Policy

Subject:	Thymus Tissue Transplantation		
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Description/Scope

This document addresses thymus tissue transplantation (also known as culture thymus tissue [CTT] transplantation) using allogeneic processed thymus tissue ~~-agdc~~ (allogeneic processed thymus tissue-agdc [RETHYMIC®], Enzyvant Therapeutics, Inc. Cambridge, MA) a regenerative therapy used for immune reconstitution in children with congenital athymia.

Note: This document does not address therapeutic uses of stem cells for hematopoietic indications (FDA-approved products derived from stem cells that are approved for limited use in individuals with disorders involving the hematopoietic system).

Note: For additional information on related topics, please see the applicable document:

- TRANS.00035 Therapeutic use of Stem Cells, Blood and Bone Marrow Products

Position Statement

Medically Necessary:

A single administration of allogeneic processed thymus tissue ~~-agdc (RETHYMIC)~~ is considered **medically necessary** for immune reconstitution in the pediatric population* with congenital athymia when **all** of the following criteria are met:

A. Congenital athymia is confirmed via flow cytometry as less than 50 naïve T cells/mm^3 in the peripheral blood or less than 5% of total T cells being naïve in phenotype; **and**
B. Documentation that infection control measures, including immunoprophylaxis, can reasonably be maintained until the development of thymic function is established; **and**

C. Absence of comorbidities, in the opinion of the treating clinician, that are reasonably likely to result in severe complications, including death from administration of allogeneic processed thymus tissue ~~-agdc~~ (for example, pre-existing renal impairment, or cytomegalovirus or Epstein-Barr virus infection).

***Note:** Pediatric population (generally age below 18 years of age)

Investigational and Not Medically Necessary:

Use of allogeneic processed thymus tissue ~~-agdc (RETHYMIC)~~ is considered **investigational and not medically necessary** for administration of all other uses, including but not limited to immune reconstitution in individuals with severe combined immunodeficiency.

Rationale

On October 8, 2021 Enzyvant Therapeutics received Breakthrough Therapy, Regenerative Medicine Advanced Therapy, Rare Pediatric Disease and Orphan Drug designation from the U.S. Food and Drug Administration (FDA) for administration by a one-time regenerative tissue-based surgical procedure of allogeneic processed thymus tissue-agdc (RETHYMIC) for immune reconstitution in children with congenital athymia. Allogeneic processed thymus tissue-agdc is the first approved therapy for the treatment of congenital athymia. (Product Information Label, 2021)

Prior to the availability of allogeneic processed thymus tissue ~~-agdc (RETHYMIC)~~, the standard of care for the management of congenital athymia was limited to the supportive care for this ultra-rare condition. Supportive care for management of congenital athymia (associated with complete DiGeorge syndrome) consists of antimicrobial prophylaxis to prevent bacterial, viral and fungal infections, monitoring and treatment of all infections, and protective isolation to reduce the risk of infection until the underlying immune deficiency can be corrected. Children with reduced B cell function can be treated with immunoglobulin replacement therapy to assist with B cell function. Individuals with oligoclonal T cells or elevated proliferative responsiveness to mitogens may receive immunosuppression therapy. Vaccine avoidance is considered, depending on the individual's degree of immunodeficiency and T cell function. Retrospective data identified 17 children (age range 2-53 months) worldwide who underwent transplantation of hematopoietic cells to correct severe T lymphocyte immunodeficiency resulting from complete DiGeorge anomaly. "Median survival among deceased patients (10 patients) was 7 months

after transplantation (range, 2-18 months). The overall survival rate was 41%, with a median follow-up of 5.8 years (range, 4-11.5 years)" (Janda, 2010).

The FDA biological license application for allogeneic processed thymus tissue-agdc was approved based on data from 10 prospective, single-arm, open-label studies conducted between 1993 and 2020. Markert and colleagues (2021) reported findings from these studies which enrolled 105 participants who received CTT (mean ages at CTT transplant 298 days) and are included in the full analysis set (FAS); however only 95 treatment-naïve individuals with a diagnosis of congenital athymia were included in the efficacy analysis set (EAS). The median follow-up time was 7.6 years, with the longest follow up period extending 25.5 years. The survival rate at year 1 was 77% (95% confidence interval [CI], 0.670-0.844) and 76% (95% CI, 0.657-0.834) at year 2. In the first 12 months 21 subjects died before developing naïve T cells and 1 died in the second year after receipt of CTT. The investigators deemed 3 subsequent deaths unrelated to immunodeficiency. Beyond 2 years no deaths occurred related to CTT. Among trial participants, immune reconstitution sufficient to prevent infections developed 6 to 12 months after implantation of allogeneic processed thymus tissue-agdc. The investigators reported a significant reduction in the number of infections over time during the first 2 years ($p<0.001$). A total of 37 participants (35%) in the CTT clinical program experienced autoimmune-related adverse events which included: thrombocytopenia (10.5%), neutropenia (7.6%), proteinuria (4.8%), hemolytic autoimmune hepatitis (1.9%), and autoimmune arthritis (1.0%). The most common adverse events (AE) in the clinical trials were hypertension (19%), cytokine release syndrome (18%), rash (15%), hypomagnesemia (16%), renal impairment/failure (12%), thrombocytopenia (12%) and graft versus host disease (10%). "AEs and infections were recorded regardless of whether they were related to the implantation procedures or underlying syndromic comorbidities. These data show the full spectrum of challenges associated with congenital athymia." In summary, Markert and colleagues concluded that in participants who were administered CTT, the treatment with CTT led to development of naïve T cells with a 1-year survival rate of 77% and a median follow-up of 7.6 years. Immune reconstitution in children with congenital athymia sufficient to prevent infections and support survival typically develops 6 to 12 months after administration of CTT.

The 2021 FDA Product Information label for allogeneic processed thymus tissue-agdc (RETHYMIC) includes the following **warnings and precautions:**

> *Infection Control and Immunoprophylaxis:*
> Immune reconstitution sufficient to protect from infection is unlikely to develop prior to 6-12 months after treatment with RETHYMIC. Given the immunocompromised condition of athymic patients, follow infection control measures until the development of thymic function is established as measured through

flow cytometry. This should include counseling patients and their caregivers on good handwashing practices and minimizing exposure to visitors

Graft Versus Host Disease:
In clinical studies with RETHYMIC, GVHD occurred in 11 (10%) RETHYMIC-treated patients of whom 6 (55%) died. RETHYMIC may cause or exacerbate pre-existing GVHD. Seven patients (7%) experienced autologous GVHD, 3 patients (3%) experienced GVHD due to maternal cells and 1 patient (1%) experienced GVHD due to cells from a prior hematopoietic cell transplant (HCT). Risk factors for GVHD include atypical complete DiGeorge anomaly phenotype, prior HCT and maternal engraftment. GVHD may manifest as fever, rash, lymphadenopathy, elevated bilirubin and liver enzymes, enteritis, and/or diarrhea.

Autoimmune Disorders:
Thirty-seven patients (35%) in the RETHYMIC clinical program experienced autoimmune-related adverse reactions. The onset of autoimmune related events ranged from the three days before the surgical implantation procedure until 16 years post-treatment. Most events occurred within the first year after treatment.

Renal Impairment:
Ten patients with renal impairment (elevated serum creatinine at baseline) were treated in studies with RETHYMIC. Five of these patients died within 1 year and a sixth patient died 3 years after treatment with RETHYMIC. Renal impairment at baseline is considered a risk factor for death.

Cytomegalovirus Infection:
In clinical studies with RETHYMIC, 3 out of 4 patients with preexisting CMV infection prior to treatment with RETHYMIC died. The benefits/risks of treatment should be considered prior to treating patients with pre-existing CMV infection.

Malignancy:
Because of the underlying immune deficiency, patients who receive RETHYMIC may be at risk of developing post-treatment lymphoproliferative disorder (blood cancer). The infant tissue donor is screened for Epstein-Barr virus (EBV) and cytomegalovirus (CMV), but patients should be tested for EBV and CMV using PCR prior to and 3 months following treatment with RETHYMIC, or after any exposure to or suspected infection with CMV or EBV.

Transmission of Serious Infections and Transmissible Infectious Diseases:
The FDA label also notes that RETHYMIC is not indicated for the treatment of patients with severe combined immunodeficiency (SCID). In the clinical program, two patients with SCID were treated in the RETHYMIC clinical program. One patient died two years after receiving RETHYMIC, and the other patient died three years after receiving RETHYMIC.

There is an ongoing expanded access study evaluating thymus transplantation safety-efficacy at Duke University (NCT01220531). Thymus transplantation with cultured thymus tissue offers children with congenital athymia with immunodeficiency and immune dysregulation a treatment option, when used in place of supportive care.

Background/Overview

Congenital athymia is considered an ultra-rare inherited condition in children, who are born without a thymus and suffer profound T cell deficiency, occurring in approximately 20 live births in the U.S each year. Clinical manifestations in congenital athymia include T cell immunodeficiency, recurrent and persistent infections, and autologous GVHD which contributes to the increased risk of mortality and increased susceptibility to infection in these individuals. Congenital athymia is associated with several genetic and syndromic disorders including FOXN1 deficiency, 22q11.2 deletion, CHARGE Syndrome (Coloboma, Heart defects, Atresia of the nasal choanae, Retardation of growth and development, Genitourinary abnormalities, and Ear anomalies), and either typical or atypical Complete DiGeorge Syndrome (Collins, 2021). The known genetic mutations associated with congenital athymia include 22q11.2 deletion, and mutations in chromodomain helicase DNA binding protein 7 (CHD7), Forkhead Box Protein N1 (FOXN1), T Box transcription factor 1 and 2 (TBX1), (TBX2) and Paired Box 1 (PAX1). T cell deficiency is normally identified during newborn screenings for SCID required in the United States. Despite optimal supportive care, children with congenital athymia typically die by age 2 or 3 due to infection or immune dysfunction.

In 2021, Gupton and colleagues provided guidance for the best practices for management of congenital athymia in children both before and after CTT, including criteria for diagnosis and genetic findings of congenital athymia:

Criteria for the diagnosis of athymia

Criteria required for the diagnosis of athymia

- Total CD3 T cells < 50/mm^3 OR naïve T cells < 50/mm^3 or naïve T cells < 5% of total T cells

- Presence of B and NK cells
- Absence of SCID genetic defects based on SCID genetic panel or whole exome sequencing
  - Thymic organoid cultures may be used if diagnosis is unclear due to phenotype

Antibodies used to detect naïve T cells

- CD45RA x CD45RO
- CD45RA x CD62L
- CD45RA x CD31

Genetic findings in congenital athymia

Genetic Defect	Test
22q11.2 deletion syndrome	Chromosome microarray, fluorescence in situ hybridization (FISH) for deletions
Recurrent microdeletions at chromosome 2p11.2	Chromosome microarray, fluorescence in situ hybridization (FISH) for deletions
Chromodomain helicase DNA binding protein 7 (CHD7), CHARGE syndrome (coloboma, heart defects, choanal atresia, growth or mental retardation, genital abnormalities, and ear abnormalities and/or deafness)	Whole-exome sequencing or sequencing of CHD7
Forkhead box N1 (Foxn1)	Whole-exome sequencing
T-box transcription factor 1 (TBX-1)	Whole-exome sequencing
T-box transcription factor 2 (TBX-2)	Whole-exome sequencing
Paired box 1 (PAX1)	Whole-exome sequencing
Semaphorin 3 (SEMA3E)	Whole-exome sequencing
10p deletions	Chromosome microarray, fluorescence in situ hybridization (FISH) for deletions

Thymus tissue transplantation using allogeneic processed thymus tissue-agdc (recommended dose range 5000 to 22,000 mm^2 of RETHYMIC surface area/m^2 recipients body surface area [BSA]) is done as a single open surgical procedure performed under general anesthesia. The surgeon makes a longitudinal incision over the anterior muscle compartment of the thigh, then implants thymus graft within furrows created within the muscle. Each furrow is then

oversewn to assist with fixation and postoperative localization. Care is taken postoperatively to monitor for compartment syndrome. Immunosuppressive medications are recommended after administration of allogeneic processed thymus tissue-agdc tissue based on disease phenotype and phytohemagglutinin (PHA) levels.

Definitions

Congenital athymia: An ultra-rare condition in children born without a thymus which results in life-threatening immunodeficiency.

DiGeorge Syndrome (also known as 22q11.2 deletion syndrome): A common form of severe combined immunodeficiency secondary to congenital athymia which is characterized by T-cell immunodeficiency, congenital heart disease, and hypocalcemia from hypoparathyroidism; the atypical phenotype is characterized by oligoclonal T-cells, lymphadenopathy and rash.

Forkhead Box Protein N1 (FOXN1) deficiency: A rare, genetic, primary immunodeficiency due to a defect in adaptive immunity characterized by the triad of congenital athymia, congenital alopecia totalis and nail dystrophy (GARD, 2017).

Graft-versus-host disease: A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

Severe combined immunodeficiency (SCID): An inherited immune system disorders characterized by abnormalities with responses of both T cells and B cells (GARD, 2017).

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:
For the following procedure codes; or when the code describes implantation or provision of RETHYMIC

CPT

27599	Unlisted procedure, femur or knee [when specified as implantation of RETHYMIC into quadriceps muscle]

HCPCS

L8699	Prosthetic implant, not otherwise specified [when specified as allogeneic processed thymus tissue-agdc (RETHYMIC) implant]

ICD-10 Diagnosis

All diagnoses

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above when criteria are not met.

References

Peer Reviewed Publications:

1. Collins C, Sharpe E, Silber A, Kulke S, Hsieh EWY. Congenital Athymia: Genetic Etiologies, Clinical Manifestations, Diagnosis, and Treatment. J Clin Immunol. 2021 Jul;41(5):881-895. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8249278/. Accessed on November 29, 2021.
2. 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.
3. Janda A, Sedlacek P, Honig M, et al. Multicenter survey on the outcome of transplantation of hematopoietic cells in patients with the complete form of DiGeorge anomaly. Blood. 2010; 116(13):2229-2236.
4. Markert ML, Gupton SE, McCarthy EA. Experience with cultured thymus tissue in 105 children. J Allergy Clin Immunol. 2021; S0091-6749(21)01056-3.

Government Agency, Medical Society, and Other Authoritative Publications:

1. National Institutes of Health (NIH). Thymus transplantation safety-efficacy. NLM Identifier: NCT01220531. Last updated: August 25, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT01220531. Accessed on November 29, 2021.
2. RETHYMIC (allogenic processed thymus tissue-agdc). Cambridge MA: Enzyvant Therapeutics, Inc. October 2021. Available at: https://www.fda.gov/vaccines-blood-biologics/rethymic. Accessed on November 29, 2021.

Websites for Additional Information

1. National Institute of Health (NIH). Genetic and Rare Diseases. Immune Defect due to absence of thymus. Available at: https://rarediseases.info.nih.gov/diseases/7201/immune-defect-due-to-absence-of-thymus. Accessed on November 29, 2021.
2. National Institute of Health (NIH). Genetic and Rare Diseases Information Center. Browse A-Z. Available at: https://rarediseases.info.nih.gov/diseases/browse-by-first-letter/F. Accessed on December 6, 2021.
    - 22q11.2 deletion syndrome. Last updated May 1, 2017.
    - FOXN1 deficiency. Last updated February 1, 2021.
    - Severe combined immunodeficiency. Last updated June 28, 2017.

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Allogeneic Processed Thymus Tissue ~~adgc~~
Complete DiGeorge Syndrome
Congenital Athymia
RETHYMIC
Thymus Transplantation

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	02/17/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.