Medical Coverage Policy

Effective Date.....8/15/2024
Next Review Date.....8/15/2025
Coverage Policy Number..... 0561

Thymus Tissue Transplantation

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses thymus tissue transplantation (also referred to as cultured thymus tissue [CTT], Rethymic®, allogenic processed thymus tissue-agdc, allogenic thymocyte-depleted thymus tissue-agdc).

Coverage Policy

A single administration of thymus tissue transplantation is considered medically necessary in a pediatric individual (age 17 and under) when the following criteria are met:

- congenital athymia, including complete DiGeorge anomaly (cDGA) or FOXN1 deficiency
- T-cell count lower than 50/mm^3 or naive T-cell (CD3+CD4+CD45RA+CD62L+ or CD3+CD8+CD45RA+ CD62L+ cells) count lower than 50/mm^3
- absence of genetic defects associated with severe combined immunodeficiency (SCID)

Thymus tissue transplantation is considered not medically necessary for all other indications, including but not limited to immune reconstitution in individuals with severe combined immunodeficiency (SCID).

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

General Background

Congenital athymia is a rare disease characterized by the absence of a functioning thymus. It is associated with several genetic and syndromic disorders including but not limited to DiGeorge syndrome. 22q11.2 deletion-associated with DiGeorge Syndrome (DGS) is the most commonly described genetic defect associated with congenital athymia; however, FOXN1, PAX1, and others have also been identified as potentially causative. The term 22q11.2 deletion syndrome covers terms once thought to be separate conditions, including DiGeorge syndrome, velocardiofacial syndrome and other disorders that have the same genetic cause, though features may vary slightly. Medical problems commonly associated with 22q11.2 deletion syndrome include conotruncal cardiac anomalies, hypoplastic thymus, and hypocalcemia (resulting from parathyroid hypoplasia).

Thymic hypoplasia in DiGeorge syndrome (DGS) results in a range of T cell deficits. Most patients with DGS have mild defects in T cell numbers and are not clinically immunodeficient. Approximately 1 percent, however, have a complete absence of thymic tissue and profound immunodeficiency. This form of DGS, called complete DGS, is a type of severe combined

immunodeficiency (SCID) and is life threatening. With only supportive care, children with congenital athymia typically do not survive beyond 2 to 3 years of age.

Screening for congenital athymia
Congenital athymia can be detected when newborns are screened for severe combined immunodeficiency (SCID). In the United States, SCID screening has become the standard method by which congenital athymia is detected. The diagnosis is confirmed by using flow cytometry in conjunction with testing for genes causing SCID. Infants with congenital athymia have very low naive T-cell counts. There is no uniformly agreed-on level of naive T cells defining congenital athymia.

Thymus Tissue Transplantation
Thymus transplantation (cultured thymus tissue [CTT] implant) is a proposed treatment for pediatric patients with profound primary immune deficiency due to primary athymia and the resulting lack of functional T cells. A pediatric surgeon transplants the cultured postnatal allogeneic thymus tissue slices into the quadriceps muscles of the athymic recipient in the hospital operating room. The surgeon creates individual pockets in the quadriceps muscle for each tissue slice, utilizing both quadriceps muscles. Recipient bone marrow stem cells migrate to the allograft where they develop into naïve T cells. Thymopoiesis is observed in biopsies of the transplanted thymus within 2 months of transplantation and naïve T cells are detected in the peripheral blood approximately 3–5 months after transplantation.

U.S. Food and Drug Administration (FDA)
The FDA granted Biologics License Application (BLA) approval on 10/08/2021 to Enzyvant Therapeutics, Inc. for Rethymic, for the treatment of pediatric patients with congenital athymia. Their application was also granted a Rare Pediatric Disease Priority Review Voucher by the FDA.

Enzyvant Therapeutics is authorized to manufacture the product Rethymic, human allogeneic (donor-derived) thymus tissue that is processed and cultured (thymus tissue-agdc, cultured thymus tissue [CTT]) and then implanted into patients to help reconstitute immunity in patients who are athymic. Dosing is patient customized, determined by the surface area of the Rethymic slices and the body surface area of the patient.

Rethymic is not indicated for the treatment of patients with severe combined immunodeficiency (SCID).

Literature Review
The safety and efficacy of Rethymic were established in clinical studies that included 105 patients, with ages from one month to 16 years, who each received a single administration of Rethymic, from 1993 – 2020 (National Clinical Trial numbers NCT00576407, NCT00576836, NCT00579527, and NCT01220531). Rethymic improved survival of children with congenital athymia, and most children treated with this product survived at least two years. Children treated with Rethymic who survive past the first year generally survive long-term. Rethymic also reduced the frequency and severity of infections over time (FDA News release, October 08, 2021).

Markert et al. (2022) reported on 105 patients treated with cultured thymus tissue (CTT), from ten prospective, single-arm open-label studies. Patient enrollment was from 1993 to 2020 at Duke University in Durham, NC.
Congenital athymia was defined in the protocols as any of the following: cDGA in which patients had athymia plus either a congenital heart defect or hypocalcemia/hypoparathyroidism or FOXN1 deficiency. cDGA included 22q11.2ds, CHARGE syndrome, other genetic defects associated with congenital athymia, and diabetic embryopathy.

Key eligibility criteria: complete DiGeorge anomaly (cDGA) or FOXN1 deficiency, T-cell count lower than 50/mm3 or naive T-cell ($CD3^+CD4^+CD45RA^+CD62L^+$ or $CD3^+CD8^+CD45RA^+$ $CD62L^+$ cells) count lower than 50/mm^3 and the absence of genetic defects associated with SCID. Patients enrolled under the expanded access protocol could have naive T-cell counts higher than 50/mm^3.

For inclusion, patients had to have athymia with a circulating $CD3^+CD45RA^+CD62L^+$ T-cell count lower than 50/mm^3 or less than 5% of the total T-cell count on 2 separate flow cytometry analyses (1 performed within 3 months and 1 performed within 1 month before administration of cultured thymus tissue [CTT]), unless they were enrolled in the expanded access protocol, according to which the naive T-cell could be higher than 50 mm^3. Patients with typical and atypical phenotypes were included.

The exclusion criteria included heart surgery within 4 weeks before administration of CTT or anticipated within 3 months after administration of CTT, poor surgical candidacy as determined by the surgeon or anesthesiologist, HIV infection, prior attempts at immune reconstitution, ventilator dependence, and cytomegalovirus (CMV) infection for patients requiring immunosuppression.

Participation: A total of 105 patients were enrolled in the study and are included in the full analysis set (FAS); 95 of these are included in the efficacy analysis set (EAS). Ten patients were excluded from the EAS: 2 because their ultimate diagnosis was SCID, 6 because they received a previous HSCT or fetal transplant, and 2 because their diagnoses were not definitive. The mean patient ages at the time of CTT administration were 298 days and 493 days for the EAS and the FAS, respectively. Of the 95 patients with congenital athymia in the EAS, 93 had the protocol-defined diagnosis of cDGA and 2 had a diagnosis of FOXN1 deficiency. Of the 105, Race was reported as follows: 72.4% White, 20 % Black, and 7.6 % other. Of the 105, Ethnicity was reported as follows: 19% Hispanic or Latino, 81% not Hispanic or Latino.

The median follow-up time for the EAS was 7.6 years and ranged from 0 to 25.5 years after receipt of CTT.

Survival rates for the EAS at year 1 and year 2 after receipt of CTT were 77% and 76%, respectively. For patients who were alive 1 year after receipt of CTT, the estimated survival rate at a median follow-up time of 10.9 years was 93%. Of 105 patients, there were 32 patients with at least 1 severe adverse event (AE), 35 patients with at least 1 life-threatening AE, and 26 AE-related deaths. Among 105 patients, there were 28 deaths; 26 were considered related to AEs and 2 others were reported after patients were withdrawn from the study because of an SCID diagnosis following administration of CTT. Of the 28 deaths, 22 (including 12 of the 13 infection-related deaths) occurred in the first year after administration of CTT, while the patients were still immunodeficient.

Davies et al. (2017) reported results on 12 patients in a single center in the UK. Evidence of thymopoiesis developed from 5 to 6 months after transplantation in 10 patients. At a median of 49 months (range, 22-80 months), 8 have ceased prophylactic antimicrobials, and 5 have ceased immunoglobulin replacement. Histologic confirmation of thymopoiesis was seen in 7 of 11 patients undergoing biopsy of transplanted tissue. Two patients died of pre-existing viral infections without having thymopoiesis, and 1 late death occurred from autoimmune thrombocytopenia. One infant had septic shock shortly after transplantation, resulting in graft loss and the need for a second transplant.

Professional Societies/Organizations
Clinical Immunology Society (CIS): The CIS Clinical Practice Guidelines for the Immunological Management of Chromosome 22q11.2 Deletion Syndrome and Other Defects in Thymic

Development (Mustillo, et al., 2023) addresses Congenital Athymia and Thymic Implant but does not make any specific recommendations.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD		No Determination found	
LCD		No Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
27599	Unlisted procedure, femur or knee

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals
J3590	Unclassified biologics

ICD-10-CM Diagnosis Codes	Description
D82.1	Di George's syndrome
Q89.2	Congenital malformations of other endocrine glands

References

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14. U. S. Food and Drug Administration (FDA) Press Announcements. FDA Approves Innovative Treatment for Pediatric Patients with Congenital Athymia. October 08, 2021. Accessed June 2024. Available at URL address: https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-treatment-pediatric-patients-congenital-athymia#:~:text=The%20safety%20and%20efficacy%20of,Rethymic%2C%20from%201993%20%E2%80%93%202020

Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	• No clinical policy statement changes.	8/15/2024