Optum

Allogeneic Processed Thymus Tissue-agdc (Rethymic®)

Clinical guideline

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Introduction

Rethymic ® is composed of cultured thymus tissue (CTT) that is processed to preserve thymic epithelial cells and deplete most of the donor thymocytes prior to being implanted into pockets made in the recipient's quadriceps muscle. CTT acts similarly to normal thymus tissue to produce immunocompetent naïve T cells (CD3+ CD4+ CD45RA+ CD62L+ and CD3+ CD8+ CD45RA+ CD62L+ cells) that can migrate into the periphery and fight infection as CD3+CD4+ or CD3+CD8+ cells. After a CTT transplant, the recipient bone marrow stem cells go to the transplanted tissue to develop into recipient T cells. The recipient dendritic cells delete any developing thymocytes that bind too tightly to dendritic cells or donor thymic epithelium in the CTT. No T cells that will attack the recipient or the CTT leave the thymus. Naïve T cells appear in the peripheral blood usually between 6- and 12-months post implantation (Markert, 2022).

Rethymic ® dosage is determined by the total surface area of the tissue slices and the recipient's body surface area (BSA). A slice is defined as the contents on a single filter membrane. The recommended dose range is 5,000 to 22,000 mm^2 of Rethymic surface area per m^2 recipient BSA. Up to 42 slices are supplied in a single-dose unit according to the dosage calculated in advance by the manufacturer for the specific patient (FDA, Rethymic® Full Prescribing Information, 2021).

Markert and colleagues (2022) demonstrated efficacy in 10 prospective, single-center, open-label studies from 1993 to 2020. A total of 105 patients were enrolled and received CTT transplants. Of those, 10 patients had diagnoses other than congenital athymia and/or received prior treatments. Of the 105 patients, 95 were included in the primary efficacy set. For inclusion, patients had to have athymia as defined by flow cytometry demonstrating 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 CTT), unless they were enrolled in the expanded access protocol, according to which the naïve T cell count could be higher than 50mm^3. Other key eligibility criteria included cDGA or FOXN1 deficiency and the absence of genetic defects associated with SCID. Exclusion criteria included heart surgery within 4 weeks before administration of CTT, poor surgical candidacy as determined by surgeon or anesthesiologist, HIV infection, prior attempts at immune reconstitution, ventilator dependence, and cytomegalovirus (CMV) infection for patients requiring immunosuppression. Immunosuppression was given to patients on the basis of proliferative response to phytohemagglutinin (PHA), regardless of typical or atypical phenotype.

Of the 95 patients with congenital athymia in the efficacy analysis set (EAS), 93 had the protocol-defined diagnosis of cDGA and 2 had FOXN1 deficiency. Kaplan-Meier estimated survival rates for EAS at 1-year and 2-years after receipt of CTT were 77% and 76%, respectively. The median follow-up time for the EAS was 7.6 years and ranged from 0 to 25.5 years. 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%. Median T-cell counts reached their peak at approximately 1-2 years after CTT transplant. Naïve T-cell numbers started at 0 in all patients and increased to their highest numbers in year 2. T-cell function was studied by proliferative responses to mitogens and antigens. B-cell and NK cell counts remained in the normal range in most patients and almost all patients were able to stop IgG replacement therapy (Markert, 2022).

Of 105 patients, there were 32 patients with at least 1 severe adverse event, 35 with at least 1 life-threatening adverse event, and 26 adverse event -related deaths. In all, 53 patients had infections categorized as severe, 13 categorized as life-threatening, and 11 had fatal infections. A total of 78 new viral infections were reported in the first year after CTT transplant. There were a total of 28 deaths among the 105 patients; 26 were considered related to adverse events and 2 others were reported after patients were withdrawn from the study because of an SCID diagnosis following CTT transplant. Of the 28 deaths, 22 (including 12 of the 13 infection-related deaths) occurred in the first year following transplant, while the patients were still immunodeficient. Respiratory failure was responsible for

10 deaths and there were 5 patients for whom bleeding was a major concern and contributed to their deaths (Markert, 2022).

Rethymic® is currently manufactured at the Marcus Center for Cellular Cures (Duke University School of Medicine, Durham, NC) and administered in an operating suite at Duke University Medical Center.

FDA Approval

In October 2021, the U.S. Food and Drug Administration (FDA) approved allogeneic processed thymus tissue-agdc (Rethymic®) for immune reconstitution in pediatric patients with congenital athymia.

Indication

Congenital athymia is an ultra- rare pediatric immune disorder characterized by the absence of a thymus with an estimated incidence of 17 to 24 infants per 4 million live births annually (Collins, 2021). Congenital athymia results in profound immunodeficiency and immune dysregulation and is usually associated with several underlying genetic and syndromic conditions including complete DiGeorge anomaly (cDGA) , 22q11.2 deletion syndrome, CHARGE (coloboma, heart defect, choanal atresia, growth or mental retardation, genital hypoplasia, and ear anomalies or deafness) syndrome, forkhead box protein N1 (FOXN1) deficiency and diabetic embryopathy. Comorbidities of these syndromes include hypoparathyroidism, heart and kidney defects, esophageal and tracheal atresia, choanal atresia, and developmental delay (Markert et al., 2022). Similar to a phenotype of severe combined immunodeficiency (SCID), athymic infants often present with absent T cells but normal numbers of B cells and Natural Killer (NK) cells, making it critical to distinguish athymia from SCID as treatments differ. In the United States, newborn SCID screening has become the standard method for detecting congenital athymia. Flow cytometry along with testing for the genes responsible for SCID are required to confirm a diagnosis of congenital athymia. (Collins et al., 2021).

Characteristics of congenital athymia include profound T cell deficiency, susceptibility to opportunistic infections, and predisposition to develop autologous graft-versus-host disease (GVHD). Autologous GVHD is the term used to refer to auto-reactive T cells that escaped T cell selection due to lack of thymus. These T cells frequently produce a cellular infiltrate and organ damage (Collins et al., 2021). Infants with congenital athymia must not receive immunizations prior to immune reconstitution as live vaccines may be fatal.

Caregivers of children with congenital athymia report substantial and wide-ranging burdens including life-threatening clinical manifestations, the emotional toll of constant fear their child may die, social isolation, and financial impact of loss of income as parents give up or take time off from work to care full time for their child (Hsieh et al., 2021). Owing to the lack of curative treatment, children with congenital athymia generally do not survive beyond early childhood. Hematopoietic stem cell transplants have been attempted in the past with very few patients surviving. Until recently, supportive care including immunoglobulin replacement, prophylactic antimicrobials, and protective isolation was the only available treatment (Markert et al., 2022).

Treatment

Transplantation of allogeneic processed thymic tissue-agdc (Rethymic®) may be considered medically necessary when one of the following criteria are met:

- Member has congenital athymia associated with one of the following diagnoses:
    - FOXN1 deficiency
    - Complete DiGeorge syndrome (cDGS), also referred to as complete DiGeorge anomaly (cDGA)
    - 22q11.2 deletion
    - CHARGE Syndrome

AND

        - a circulating T cell count on flow cytometry demonstrating fewer than 50 naïve T cells/mm^3 (CD45RA+ CD62L+) in the peripheral blood.

OR

        - less than 5% of the total T cells being naïve in phenotype.

AND

- All of the following criteria are met:
    - Severe combined immunodeficiency (SCID) has been conclusively ruled out by the absence of SCID-causing genetic defects.
    - Member has not previously received thymus tissue transplantation in his or her lifetime.
    - Dosage will not exceed a single, one-time dose up to 22,000 mm^2 of Rethymic surface area per m^2 recipient body surface area (BSA), not to exceed 42 slices as calculated and supplied by the manufacturer.

References

Collins C, Kim-Chang JJ, Hsieh E, et al. Economic burden of congenital athymia in the United States for patients receiving supportive care during the first 3 years of life. J Med Econ. 2021 Jan-Dec;24(1):962-971. doi: 10.1080/13696998.2021.1962129. PMID: 34324414.

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U. S. Food and Drug Administration. Center for Drug Evaluation and research. (2021). Rethymic (allogeneic processed thymus tissue-agdc) Full Prescribing Information. Accessed 09/22/2023. Available at: Package Insert - RETHYMIC. (fda.gov)

Review and Approval History

Version	Date of annual review
1.0	05/05/2022: New Clinical Guideline. Approved by Medical Technology Advisory Committee.
2.0	10/17/2023. Annual review. Transferred to new template. Approved by Optum Clinical Guideline Advisory Committee.
2.0	12/7/2023: Approved by Medical Technology Advisory Committee.