Clinical Policy Title: Alemtuzumab induction therapy in lung transplantation

Clinical Policy Number: CCP.1288

Effective Date: March 1, 2017
Initial Review Date: February 15, 2017
Most Recent Review Date: February 5, 2019
Next Review Date: February 2020

Related policies:
CCP.1202 Lung transplants

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of alemtuzumab as induction therapy in lung transplantation to be investigational and, therefore, not medically necessary (Saldanha, 2015; Penninga, 2013).

For any determinations of medical necessity for medications, refer to the applicable state approved pharmacy policy.

Limitations:

This policy does not address alemtuzumab as treatment for B-cell chronic lymphocytic leukemia, multiple sclerosis, or other solid organ transplantation.

Effective September 4, 2012, alemtuzumab, marketed as Campath® (Genzyme Corporation, Cambridge, Massachusetts), is no longer available commercially and therefore is not eligible for reimbursement. It may be provided through the Campath Distribution Program free of charge. Please contact the manufacturer.
Alternative covered services:

Conventional maintenance immunosuppression comprising anti-proliferative agents, calcineurin inhibitors, and corticosteroids.

Background

Lung transplantation is a treatment of last resort for end-stage lung disease. The most common indications for lung transplantation are advanced chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis, emphysema due to alpha-1 antitrypsin deficiency, and pulmonary arterial hypertension (Yusen, 2015).

In the United States, 2,327 lung transplantations were performed in 2016 (Organ Procurement and Transplant, 2017). Among those age 12 and older, 57.1 percent of transplants were performed for a diagnosis of a restrictive lung disease, 26.1 percent were performed on those with an obstructive lung disease, 12.0 percent were performed on those with cystic fibrosis, and 4.0 percent were performed for pulmonary vascular disease (Valipour, 2018). For persons with cystic fibrosis, contemporary registry analyses have confirmed a survival disadvantage among children compared to adults after lung transplantation (Hayes, 2016a; Moreno, 2016). While the proportion of lung transplantations performed for cystic fibrosis has decreased significantly over time, especially in pediatric patients, proportions are increasing in patients who are older and more clinically ill (Kinmura, 2016; Moreno, 2016).

Acute and chronic allograft rejection limit long-term graft and patient survival, with a median survival of approximately six years after lung transplantation (Yusen, 2015). Immunosuppressive regimens, consisting of maintenance and induction therapies, are used to reduce graft failure. Conventional maintenance immunosuppression is lifelong therapy comprising anti-proliferative agents, calcineurin inhibitors, and corticosteroids. These drugs primarily target T-cell activation and proliferation involved in cell-mediated rejection, but they are associated with serious adverse effects, including drug-specific toxicities, opportunistic infections, and malignancy (Scheffert, 2014; Yusen, 2015).

Approximately 50 percent of lung transplant centers use induction therapy (Scheffert, 2014). Induction therapy is intensive immunosuppressant therapy given peri-operatively to cause significant T-cell depletion immediately after transplantation. The aim of induction therapy is to reduce the risk of acute rejection and delay initiation of maintenance therapy following transplantation, particularly the nephrotoxic calcineurin inhibitors. Induction therapy is usually administered for a short period of time to avoid risks of severe infection and sepsis. Drugs used in induction immunosuppression after lung transplantation include polyclonal antibody preparations (anti-thymocyte globulin), interleukin 2 receptor antagonists (daclizumab or basiliximab), or alemtuzumab (Scheffert, 2014).

Alemtuzumab:

Alemtuzumab is a recombinant humanized monoclonal antibody that binds to the CD52 glycoprotein located on the cell surface of mature T-lymphocytes and B-lymphocytes. The mechanism of action is
believed to recruit antibodies that target and destroy the CD52-bearing lymphocytes treated with alemtuzumab, thereby depleting circulating T- and B-cells and improving graft survival. Originally, the U.S. Food and Drug Administration approved alemtuzumab as Campath in 2001 for treatment of B-cell chronic lymphocytic leukemia (Food and Drug Administration, 2016). Campath was discontinued commercially in 2012, but remains available through the Campath Distribution Program free of charge (Campath, 2016).

In 2014, the Food and Drug Administration approved alemtuzumab as Lemtrada™ (Genzyme Corporation, Cambridge, Massachusetts) for treatment of individuals with relapsing forms of multiple sclerosis who have had an inadequate response to two or more drugs indicated for the treatment of multiple sclerosis (Food and Drug Administration, 2016). Its mechanism of action may have value as an immunosuppressive agent in solid organ transplantation. Alemtuzumab as induction therapy in lung transplant recipients is an off-label use.

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.
- Cochrane Reviews.

We conducted searches on December 20, 2018. Search terms were: "alemtuzumab" (Supplementary Concept), lung transplantation" (MeSH), and free text terms "alemtuzumab induction" and "lung transplant."

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

No professional medical society guidelines addressing alemtuzumab as an induction agent in lung transplantation have been published.

We found two Cochrane reviews for this policy (Saldanha, 2015; Penninga, 2013). Neither review identified any randomized controlled trials of alemtuzumab as induction therapy in lung transplantation recipients.
Results from individual retrospective cohort studies and registry analyses provide conflicting evidence of the relative safety and efficacy of alemtuzumab induction therapy in this population (Hayes, 2014; Kirby, 2015; Jaksch, 2014; Shyu, 2011; Wehman, 2013; Whited, 2015).

Several risk factors are significantly associated with mortality during the first post-transplant year. These risk factors include recipient age; severity of illness and cytomegalovirus status of the recipient; indication for transplant; era in which the transplant was performed; and type of transplant (Yusen, 2015).

Retrospective analyses failed to account for these factors, which may contribute to the variability in outcomes. Therefore, there is insufficient evidence to determine the safety or efficacy of alemtuzumab as induction therapy in lung transplantation recipients. Robust randomized controlled trials are needed to assess the role of alemtuzumab compared to no induction therapy or to other induction therapy agents.

Policy Updates:

A total of five peer-reviewed references were added to this policy in December 2018. These include the following:

A study of 12,858 adult deceased lung transplantation patients compared outcomes for 5713 given induction (62 percent given basiliximab, 14 percent given alemtuzumab, and 24 percent given another agent) and 7,145 who did not. The induction group had significantly increased overall survival (71.3 months versus 63.2 months, \( P < .0001 \)). Basiliximab and alemtuzumab had the highest median survival times at 75.1 months and 75.5 months (Whitson, 2014).

Rescue alemtuzumab was given to 51 patients after lung transplantation for refractory acute cellular rejection or bronchiolitis obliterans syndrome, with 722 days as the median time to rescue. Composite rejection standardized score declined significantly \( (P < .001) \) after rescue. Freedom from ≥A2 was 62.5 percent in the refractory acute cellular rejection cohort, while freedom from bronchiolitis obliterans syndrome progression was 52.9 percent at 180 days in the BOS cohort. Infections developed in 72.5 percent and 76.5 percent of the two groups. Authors state that rescue alemtuzumab appears useful for refractory acute cellular rejection, but not for bronchiolitis obliterans syndrome (Ensor, 2017).

A study of 6117 double lung transplant patients compared 738 who received alemtuzumab, 2804 who received basiliximab, and 2575 who received no induction. Alemtuzumab recipients had higher lung allocation scores (41.4 versus 37.9 versus 40.7, \( P < .001 \)) and were more likely to require mechanical ventilation before to transplantation (21.7 percent versus 6.5 percent versus 6.2 percent, \( P < .001 \)). Median survival was longer for alemtuzumab and basiliximab recipients (2321 versus 2352 versus 1967 days, \( P = .001 \)). After five years, alemtuzumab recipients had a significantly lower incidence of bronchiolitis obliterans syndrome (22.7 percent versus 55.4 percent versus 55.9 percent). Both therapies improved survival, but alemtuzumab patients had greater median freedom from bronchiolitis obliterans syndrome (Furuya, 2016).

A study of 3,405 patients undergoing lung transplantation for chronic obstructive pulmonary disease included 1,644 with no induction therapy, plus 1,146 given basiliximab, 380 given alemtuzumab, and 235 given a polyclonal preparation. Induction therapy patients had a significantly better hazard ratio \( (P = .001) \).
Induction therapy had a protective influence with respect to delayed onset of bronchiolitis obliterans syndrome after transplant ($P = .003$). No difference in death risk from infection was observed (Duffy, 2016).

A study of 14,578 first-time adult lung transplant recipients included a comparison of hazard of bronchiolitis obliterans syndrome by type of Induction. Alemtuzumab had the superior hazard ratio ($0.343; P < .001$), but basiliximab was also significant ($0.862; P = .023$) (Hayes, 2016b).

Of 23,951 lung transplants in a data base, only 330 were pediatric cases, and only three of these were given alemtuzumab as an induction agent, too few from which to draw significant conclusion (Hayes, 2014).

A review of 336 adult lung recipients included four groups given induction, including alemtuzumab (n= 127), thymoglobulin (n = 43), daclizumab (n = 73), and none (n = 93). Alemtuzumab had the highest combined patient/graft survival rates of any group, at 59 percent for both. Alemtuzumab also had the greatest five-year freedom, compared to the other groups, from acute cellular rejection (30 percent), lymphocytic bronchiolitis (82 percent), obliterative bronchiolitis (86 percent), and bronchiolitis obliterans syndrome (54 percent) (Shyu, 2013).

The policy number was changed from 07.02.09 to CCP.1288.

References

Professional society guidelines/other:


Peer-reviewed references:


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

No National Coverage Determinations were identified as of the writing of this policy. Several policy articles were found.

- A52474 Immunosuppressive Drugs - Policy Article.
- A55297 Billing and Coding of Drug and Biological Infusions.
- A52953 Chemotherapy Administration.
- A52991 Chemotherapy Administration.
- A54848 Drug Administration Coding.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.
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