UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immune Globulin – Atgam Utilization Management Medical Policy

- Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] intravenous infusion – Pfizer)

REVIEW DATE: 12/14/2022

OVERVIEW

Atgam, an immune globulin, is indicated for the following uses:[1]

- **Allograft rejection**, for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, Atgam increases the frequency of resolution of the acute rejection episode.
- **Aplastic anemia,** for the treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation. The usefulness of Atgam has not been demonstrated in patients with aplastic anemia who are suitable candidates for bone marrow transplantation or in patients with aplastic anemia secondary to neoplastic disease, storage disease, myelofibrosis, Fanconi's syndrome, or in patients known to have been exposed to myelotoxic agents or radiation.

Guidelines

The use of Atgam is supported in clinical guidelines in a number of situations.[2-9]

- **Acute cellular rejection**: The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Care of Kidney Transplant Recipients (2009) recommends anti-thymocyte globulin (ATG) as a treatment option for induction therapy, given prior to, at the time of, or immediately after transplant.[2] The KDIGO guidelines recommend ATG for the treatment of acute cellular rejection unresponsive to corticosteroids, recurrent acute cellular rejection, and for acute antibody-mediated rejection.
- **Aplastic anemia**: The British Society of Haematology guidelines for the diagnosis and management of aplastic anemia recommend immunosuppressive therapy with Atgam (equine ATG) plus cyclosporine for the first-line treatment of patients with non-severe aplastic anemia requiring treatment, severe or very severe aplastic anemia in those who lack a matched sibling donor, and severe or very severe aplastic anemia in patients > 35 to 50 years of age.[3,4] A second course of Atgam is recommended following a relapse after the first course of therapy, or after failure to respond to the first course if the patient is ineligible for a matched unrelated donor hematopoietic stem cell transplant. In addition, Atgam is included in conditioning regimens for bone marrow transplantation.[5]
- National Comprehensive Cancer Network (NCCN) guidelines:[6-9]
  - **Graft-vs-host disease:** The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (version 2.2022 – September 28, 2022) recommend ATG as additional therapy in conjunction with corticosteroids for the management of acute steroid-refractory disease.[9]
  - **Immunotherapy-related cardiovascular toxicity:** The NCCN Guidelines for the Management of Immunotherapy-Related Toxicities (version 1.2022 – February 28, 2022), recommend Atgam as additional treatment for severe or life-threatening myocarditis, pericarditis, arrhythmias, or impaired ventricular function, or conduction abnormalities if no improvement within 24 hours of starting pulse-dose methylprednisolone.[6,7]
  - **Myelodysplastic syndrome:** The NCCN Clinical Practice Guidelines (version 1.2023 – September 12, 2022) recommend Atgam as a treatment option for the management of lower risk disease.[7,8] Treatment with Atgam alone or in combination with cyclosporine and/or

Promacta® (eltrombopag olamine tablets) is recommended for select patients with clinically relevant thrombocytopenia, neutropenia, or increased marrow blasts; or for select patients with symptomatic anemia.

Other Uses With Supportive Evidence

One case report has been published which summarized the use of equine ATG for the treatment of a patient with fulminant myocarditis secondary to Opdivo® (nivolumab intravenous infusion) therapy.[10] Equine ATG was administered according to the local protocol for acute cellular rejection and consisted of 500 mg on Day 1 and the dose was titrated by 250 mg daily to maintain a CD2/3 level of 50 – 100/µL for a total of 5 days of treatment. Resolution of ventricular arrhythmias occurred within 3 days of beginning ATG and cardiac enzymes normalized by Day 5. Cardiac biopsy 10 days after beginning ATG treatment revealed histologic improvement with significantly less myocyte necrosis.

Atgam has been utilized as a component of induction therapy for heart and lung transplantation.[11-15] In a retrospective review of 163 consecutive patients undergoing lung transplantation, 65 patients received Atgam and 98 received daclizumab as a component of induction therapy.[11] At two years after transplantation, more patients treated with Atgam had acute rejection (28% vs. 9%, respectively) and bronchiolitis obliterans (23% vs. 6.4%). In another retrospective analysis of lung transplantation in pediatric patients (n = 330), approximately half of the patients received induction therapy and 30% of these patients received horse or rabbit ATG.[12] Overall survival in the patients who received induction therapy was numerically, but not significantly longer than the patients who did not receive induction therapy (77.4 months vs. 50.8 months, respectively). An article reviewing immunosuppression in lung transplantation states that approximately 20% of the centers that utilize induction therapy use ATG (horse or rabbit).[13] In a clinical trial, patients undergoing heart transplantation were randomized to Atgam (n = 15) or daclizumab (n = 15) as a component of induction therapy.[14] There were no differences in rejection, infection, or malignancy between groups. In addition, 1 year survival was similar between groups (87% in both groups). In a prospective trial, the safety and efficacy of Atgam (n = 21) was compared with OKT3 (n = 20) in patients undergoing heart transplantation.[15] Survival at 12 months, time to first rejection episode, and rejection rate was similar between the two groups. However, viral infections (1.6 vs. 0.8) and adverse events were significantly more common with OKT3 compared with Atgam.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Atgam. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Atgam as well as the monitoring required for adverse events and long-term efficacy, approval requires Atgam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Atgam is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Allograft Rejection in Solid Organ Transplant.** Approve for 1 month if the patient meets the following criteria (A and B):
   - **A)** Patient meets one of the following (i or ii):
     - **i.** Atgam is used for induction therapy, prior to, at the time of, or immediately following transplantation; OR
     - **ii.** Atgam is used for the treatment of acute rejection; AND
   - **B)** The medication is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** Up to 15 mg/kg administered intravenously daily for up to 14 days; AND
   - **B)** Up to seven additional doses can be administered intravenously every other day for a maximum total of 21 doses in 28 days.

2. **Aplastic Anemia.** Approve for 1 month if the patient meets the following criteria (A, B, and C):
   - **A)** Patient has moderate to severe disease; AND
   - **B)** Patient is unsuitable for bone marrow transplantation; AND
   - **C)** The medication is prescribed by or in consultation with a hematologist or a physician who specializes in the treatment of aplastic anemia.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** Up to 20 mg/kg administered intravenously daily for up to 14 days; AND
   - **B)** Additional alternate-day therapy up to a total of 21 doses may be given.

Other Uses with Supportive Evidence

3. **Allogeneic Hematopoietic Stem Cell Transplantation**. Approve for 1 month if the patient meets the following criteria (A and B):
   - **A)** Atgam is used as part of a conditioning regimen beginning prior to allogeneic hematopoietic stem cell transplantation; AND
   - **B)** The medication is prescribed by or consultation with an oncologist or a physician who specializes in allogeneic hematopoietic stem cell transplantation.

   Dosing. Approve the following dosing regimens (A and B):
   - **A)** Up to 40 mg/kg administered intravenously daily as a single dose, or divided and given twice daily; AND
   - **B)** Atgam is given for up to 4 days.

4. **Graft-Versus-Host Disease**. Approve for 1 month if the patient meets the following criteria (A, B, and C):
   - **A)** Patient has acute disease; AND
   - **B)** Patient's disease is refractory or resistant to corticosteroid therapy; AND
   - **C)** The medication is prescribed by or consultation with an oncologist or a physician who specializes in allogeneic hematopoietic stem cell transplantation.

   Dosing. Approve the following dosing regimens (A and B):
   - **A)** Up to 40 mg/kg/day administered intravenously; AND
   - **B)** Up to 10 doses can be administered in a course of therapy.

5. **Immune Checkpoint Inhibitor-Related Toxicities**. Approve for 1 month if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient has received at least one immune checkpoint inhibitor; AND
     Note: Immune checkpoint inhibitors include Opdivo (nivolumab intravenous infusion), Keytruda (pembrolizumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), Yervoy (ipilimumab intravenous infusion).
   - **B)** Patient has life-threatening myocarditis, pericarditis, arrhythmias, or impaired ventricular function, according to the prescriber; AND
   - **C)** Patient has not improved within 24 hours of starting pulse-dose methylprednisolone; AND
   - **D)** The medication is prescribed by or consultation with a cardiologist, oncologist or a physician who specializes in the treatment of immune checkpoint inhibitor-related toxicity.

   Dosing. Approve the following dosing regimens (A and B):
   - **A)** Up to 15 mg/kg administered intravenously daily for 14 days; AND
   - **B)** Up to seven additional doses can be administered intravenously every other day for a maximum total of 21 doses in 28 days.

6. **Myelodysplastic Syndrome**. Approve for 1 month if the patient meets the following criteria (A, B, and C):
   - **A)** Patient has lower risk disease; AND
     Note: Lower risk disease is defined as International Prognostic Scoring System (IPSS) risk of low or intermediate-1; IPSS-Revised (IPSS-R) risk of very low, low, or intermediate; World Health Organization Prognostic Scoring System (WPSS) risk of very low, low, or intermediate.
   - **B)** Patient has one of the following according to the prescriber (i, ii, iii, or iv):
     - **i.** Clinically relevant thrombocytopenia; OR
     - **ii.** Clinically relevant neutropenia; OR
     - **iii.** Increased marrow blasts; OR
     - **iv.** Symptomatic anemia; AND
   - **C)** The medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve up to 40 mg/kg/day administered intravenously for up to 4 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Atgam is not recommended in the following situations.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Atgam® intravenous infusion [prescribing information]. New York, NY: Pfizer; August 2021.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guidelines for the care of kidney transplant recipients. *Am J Transplant*. 2009;9:S1-S157.
3. Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. *Br J Haematol*. 2016;172:187-207.
4. Samarasinghe S, Veys P, Vora A, Wynn R. Paediatric amendment to adult BSH guidelines for aplastic anaemia. *Br J Haematol*. 2018;180:201-205.
5. Peslak SA, Olson T, Babushok DV. Diagnosis and treatment of aplastic anemia. *Curr Treat Options Oncol*. 2017;18:70.
6. The NCCN Management of Immunotherapy-Related Toxicities Clinical Practice Guidelines in Oncology (version 1.2022 – February 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 9, 2022.
7. The NCCN Drugs and Biologics Compendium. © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 9, 2022. Search term: Atgam.
8. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2023 – September 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 9, 2022.
9. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines in Oncology (version 2.2022 – September 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 9, 2022.
10. Tay RY, Blackley E, McLean C, et al. Successful use of equine anti-thymocyte globulin (ATGAM) for fulminant myocarditis secondary to nivolumab therapy. *Br J Cancer*. 2017;117:921-924.
11. Ailawadi G, Smith PW, Oka T, et al. Effects of induction immunosuppression regimen on acute rejection, bronchiolitis obliterans, and survival after lung transplantation. *J Thorac Cardiovasc Surg*. 2008;135:594-602.
12. Hayes D, Kirkby S, Wehr AM, et al. A contemporary analysis of induction immunosuppression in pediatric lung transplant recipients. *Transpl Int*. 2014;27:211-218.
13. Scheffert JL, Raza K. Immunosuppression in lung transplantation. *J Thorac Dis*. 2014;6:1039-1053.
14. Mullen JC, Kuurstra EJ, Oreopoulos A, et al. A randomized controlled trial of daclizumab versus anti-thymocyte globulin induction for heart transplantation. *Transplant Res*. 2014;3:14.
15. MacDonald PS, Mundy J, Keogh AM, et al. A prospective randomized study of prophylactic OKT3 versus equine antithymocyte globulin after heart transplantation – increased morbidity with OKT3. *Transplantation*. 1993;55:110-116.
16. Storb R, Blume KG, O'Donnell MR, et al. Cyclophosphamide and antithymocyte globulin to condition patients with aplastic anemia for allogeneic marrow transplantations: The experience in four centers. *Biol Blood Marrow Transplant*. 2001;7:39-44.
17. Hagen P, Wagner JE, DeFor TE, et al. The effect of equine antithymocyte globulin on the outcomes of reduced intensity conditioning for AML. *Bone Marrow Transplant*. 2014;49:1498-1504.
18. Pantin J, Tain X, Shah AA, et al. Rapid donor T-cell engraftment increases the risk of chronic graft-versus-host disease following salvage allogeneic peripheral blood hematopoietic cell transplantation for bone marrow failure syndromes. *Am J Hematol*. 2013;88:874-882.
19. Atta EH, Martins de Sousa A, Schirmer MR, et al. Different outcomes between cyclophosphamide plus horse or rabbit antithymocyte globulin for HLA-identical sibling bone marrow transplant in severe aplastic anemia. *Biol Blood Marrow Transplant*. 2012;18:1876-1882.
20. Durrant S, Mollee P, Morton AJ, Irving I. Combination therapy with tacrolimus and anti-thymocyte globulin for the treatment of steroid-resistant acute graft-versus-host disease developing during cyclosporine prophylaxis. *Br J Haematol*. 2001;113:217-223.
21. Khoury H, Kashyap A, Adkins DR, et al. Treatment of steroid-resistant acute graft-versus-host disease with anti-thymocyte globulin. *Bone Marrow Transplant*. 2001;27:1059-1064.
22. MacMillan ML, Weisdorf DJ, Davies SM, et al. Early antithymocyte globulin therapy improves survival in patients with steroid-resistant acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2002;8:40-46.
23. MacMillan ML, Couriel D, Weisdorf DJ, et al. A phase 2/3 multicenter randomized clinical trial of ABX-CBL versus ATG as secondary therapy for steroid-resistant acute graft-versus-host disease. *Blood*. 2007;109:2657-2662.
24. Molldrem JJ, Caples M, Mavroudis D, et al. Antithymocyte globulin for patients with myelodysplastic syndrome. *Br J Haematol*. 1997;99:699-705.
25. Yazji S, Giles FJ, Tsimberidou AM, et al. Antithymocyte globulin (ATG)-based therapy in patients with myelodysplastic syndromes. *Leukemia*. 2003;17:2101-2106.
26. Molldrem JJ, Leifer E, Bahceci E, et al. Antithymocyte globulin for treatment of the bone marrow failure associated with myelodysplastic syndromes. *Ann Intern Med*. 2002;137:156-163.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/08/2021
Annual Revision	No criteria changes.	12/14/2022