POLICY: Immune Globulin – Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] solution for intravenous use – Pfizer)

DATE REVIEWED: 12/04/2019

OVERVIEW

Atgam is derived from horses immunized with human thymus lymphocytes and is composed of antibodies to a variety of antigens on the surface of lymphocytes.[1] The exact mechanism of action of Atgam has not been determined, but may be due to the depletion of circulating lymphocytes, primarily T-lymphocytes.

Atgam is indicated for the management of allograft rejection in renal transplant patients.[1] When administered with conventional therapy at the time of rejection Atgam increases the frequency of resolution of the acute rejection episode.

Atgam is indicated for the treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation.[1] 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 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Care of Kidney Transplant Recipients (2009), recommend 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.

The British Society of Haematology guidelines for the diagnosis and management of aplastic anemia recommends immunosuppressive therapy with Atgam (equine ATG) plus cyclosporine for the first-line treatment of non-severe aplastic anemia patients requiring treatment, severe or very severe aplastic anemia patients who lack a matched sibling donor, and severe or very severe aplastic anemia patients aged > 35 – 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]

The National Comprehensive Cancer Network (NCCN) Guidelines for the Management of Immunotherapy-Related Toxicities (Version 1.2019 – November 14, 2018), recommend Atgam as a treatment option for immunotherapy-related cardiovascular toxicity due to immune checkpoint inhibitor therapy.[6,7]

The NCCN Myelodysplastic Syndromes (MDS) Clinical Practice Guidelines (Version 2.2019 – October 18, 2018) recommend Atgam as a treatment option for the management of lower risk MDS.[7,8] Lower risk is defined as International Prognostic Scoring System (IPSS) category of low or intermediate-1; IPSS-Revised (IPSS-R) category of very low, low, or intermediate; or World Health Organization Prognostic Scoring System (WPSS) category of very low, low, or intermediate. Treatment with Atgam alone or in

combination with cyclosporine is recommended for select patients with clinically relevant thrombocytopenia, neutropenia, or increased marrow blasts; or for select patients with symptomatic anemia.

The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (Version 1.2020 – October 30, 2019) recommend ATG in conjunction with corticosteroids for the management of acute steroid-refractory graft-vs-host disease.[30]

Other Uses With Supportive Evidence

The safety and efficacy of equine ATG for the management of MDS has been assessed in a variety of clinical trials.[9-15] These trials utilized equine ATG from two different manufacturers with different dosing regimens. In each of the trials with Atgam, 40 mg/kg/day for 4 days was used in the management of MDS.[9-11] In a Phase II, open-label trial ATG 40 mg/kg/day for 4 days was administered to 25 adult patients with transfusion-dependent MDS.[9] At a median of 55 days after beginning treatment with ATG, 44% of patients (n = 11/25) became red cell transfusion independent with a median duration of response of 10 months. An open-label study assessed the safety and efficacy of ATG 40 mg/kg/day for 4 days in the treatment of patients (n = 32) with MDS.[10] Patients also received cyclosporine for 6 months and methylprednisolone prior to each dose of ATG. In the 31 evaluable patients, four patients had a complete response and one had a partial response for an overall response rate of 16%. In the subgroup of patients with refractory anemia (RA) or RA with ringed sideroblasts, the overall response rate was 22% (n = 4/18), with three complete and one partial response. In a phase II, open-label study the safety and efficacy of ATG 40 mg/kg/day for 4 days was assessed in 61 MDS patients who were red blood cell transfusion dependent.[11] Within 8 months of treatment with ATG, 34% of the patients (n = 21) became transfusion independent and 80% of these patients (n = 17/21) maintained transfusion independence. In addition, responding patients had significant increases in mean platelet and neutrophil counts compared to non-responders. In the four studies utilizing a formulation of equine ATG not available in the US, the dose administered was 15 mg/kg/day for 5 days.[13-15] In these studies, between 29% and 50% of patients treated with equine ATG had a response to treatment.

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 injection for intravenous use) therapy.[16] 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.

The utility of Atgam, as part of a conditioning regimen administered prior to allogeneic hematopoietic stem cell transplant has been assessed in a number of studies.[17-25] In a study including patients with severe aplastic anemia (n = 94), cyclophosphamide and Atgam were administered as the conditioning regimen prior to bone marrow transplant.[17] Atgam 30 mg/kg/day was administered on Days 6, 5, and 4 prior to transplant. The incidence of acute and chronic GVHD was 29% and 32%, respectively and overall survival was 88% after a median of 6 years of follow-up. In a retrospective comparison, the efficacy of a reduced intensity conditioning (RIC) regimen with (n = 34) and without Atgam (n = 110) was assessed in patient undergoing umbilical cord blood or peripheral blood stem cell transplant for acute myeloid leukemia.[18] The RIC included fludarabine and cyclophosphamide. Atgam 15 mg/kg every 12 hours was administered on Days 6, 5, and 4 prior to transplant. No significant difference were found between the two RIC regimens for treatment-related mortality, acute or chronic GVHD. The group treated with Atgam did have a lower risk of relapse. In a retrospective analysis the efficacy of an RIC including cyclophosphamide, fludarabine and 4 days of Atgam 40 mg/kg/day was assessed in patients (n = 56) with bone marrow failure syndrome undergoing peripheral blood hematopoietic cell transplant.[19] Patients in the study had received extensive prior transfusion and had a high prevalence of pretransplant HLA-alloimmunization. During the study, no

graft failures occurred, overall survival was 87% after 4.5 years of follow-up, and grade II-IV acute GVHD and chronic GVHD occurred in 52% and 72% of patients, respectively. In a retrospective comparison, the efficacy of equine ATG (n = 20) was compared to rabbit ATG (n = 20) in consecutive patients undergoing bone marrow transplantation for severe aplastic anemia.[20] ATG was used as part of a conditioning regimen with cyclophosphamide. The incidence of acute grade II-IV GVHD (0% vs. 35.2%; p = 0.009) and moderate to severe chronic GVHD (0 vs. 34%; p = 0.04) were lower with rabbit ATG vs. equine ATG, respectively. However, lymphocyte counts were higher with equine ATG and overall survival was similar between groups. A number of smaller retrospective analyses including 4 to 18 patients has found similar results with the addition of Atgam to conditioning regimens administered prior to hematopoietic cell transplantation.[21-25]

The efficacy of Atgam for the treatment of steroid resistant acute GVHD following allogeneic hematopoietic cell transplant was evaluated in four studies[26-29] In a retrospective study, the efficacy of Atgam was assessed in patients (n = 20) with steroid refractory or dependent acute GVHD.[26] Patients who failed to respond or had early relapse after treatment with high-dose prednisolone (> 2 mg/kg) received Atgam 15 mg/kg/day for 5 consecutive days and tacrolimus. Grade III or IV acute GVHD was present in 90% of the patients (n = 18/20). The overall response rate (ORR) was 70% with 40% of patients (n = 8/20) achieving a complete response (CR) and 30% of patients (n = 6/20) achieving a partial response (PR). Median survival post-treatment was 86.5 days (range, 21 to 1081 days) with seven patients alive at the final assessment. In another retrospective study, the efficacy of Atgam was assessed in patients (n = 58) who either progressed after 3 days of methylprednisolone (2 mg/kg/day) or were unchanged after 7 days of methylprednisolone (2 mg/kg/day).[27] Patients received one of the following Atgam regimens: 40 mg/kg/day for 4 days, 15 mg/kg every other day for a total of 6 days, or 10 – 20 mg/kg/day for 5 to 10 days. Nearly all patients (94%, n = 54/58) had grade III or IV acute GVHD. In the 52 evaluable patients, 8% of patients (n = 4/52) had a CR, 23% of patients (n = 12/52) had a PR, mixed results occurred in 42% of patients (n = 22/52), and 27% of patients (n = 14/52) had stable disease or disease progression. Overall survival was poor, with 90% of patients (n = 52/58) dying a median of 40 days (range, 2 to 741 days) after beginning Atgam therapy. A retrospective analysis evaluated the efficacy of Atgam in patients (n = 79) who developed resistant to or progressed after receiving prednisone 60 mg/m^2 daily (or equivalent) for acute GVHD.[28] Patients received Atgam 15 mg/kg twice daily for 5 days. Grade III and IV acute GVHD occurred in 43% of the patients (n = 34/79). A durable CR, defined as a response lasting at least 28 days, was achieved by 20% of patients (n = 16), a durable PR was achieved by 34% of patients (n = 27), and no response occurred in 42% of patients (n = 33). The Kaplan-Meier estimated 1 year survival was 32% (95% confidence interval: 22%, 42%) with 25 patients alive between 1 and 9 years after treatment. A phase 2/3 trial of an investigational product for steroid-resistant acute GVHD included Atgam as the control arm of the study.[29] A total of 47 patients were randomized to the Atgam arm and received 30 mg/kg every other day for a total of 6 doses. The primary endpoint was patient survival at 180 days post randomization. Patients who had received ≥ 3 days of methylprednisolone (≥ 2 mg/kg/day) were included in the trial. Most patients had grade II or III acute GVHD. Survival probability was 47% at Day 180 with Atgam and 57% of patients (n = 27/47) achieved a CR or PR at a median of Day 22.

Atgam has been utilized as a component of induction therapy for heart and lung transplantation.[31-34] 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.[31] At two years after transplantation, more patients treated with Atgam had acute rejection (28% vs. 9%, respectively; P = 0.002) and bronchiolitis obliterans (23% vs. 6.4%; P = 0.002). 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.[32] 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; P = 0.3601). Finally, an article reviewing

immunosuppression in lung transplantation states that approximately 20% of the centers that utilize induction therapy use ATG (horse or rabbit).[33] In a clinical trial, patients undergoing heart transplantation were randomized to Atgam (n = 15) or daclizumab (n = 15) as a component of induction therapy.[34] 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.[35] 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, $P < 0.05$) 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 indication(s). 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.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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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.[1]

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2. **Aplastic Anemia.** Approve for 1 month if the patient meets the following criteria (A, B, and C).
   - **A)** The patient has moderate to severe disease; AND
   - **B)** The 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.[1]

Other Uses with Supportive Evidence

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3. Myelodysplastic Syndrome. Approve for 1 month if the patient meets the following criteria (A, B, and C):
A) The patient has lower risk disease.
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 (IPSS) risk of very low, low, or intermediate; AND
B) The 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.[9-11]

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4. Immune Checkpoint Inhibitor-Related Toxicities. Approve for 1 month if the patient meets the following criteria (A, B, C, and D):
A) The patient has received at least one immune checkpoint inhibitor.
Note: Immune checkpoint inhibitors include Opdivo® (nivolumab injection for intravenous use), Keytruda® (pembrolizumab injection for intravenous use), Tecentriq® (atezolizumab injection for intravenous use), Bavencio® (avelumab injection for intravenous use), Imfinzi® (durvalumab injection for intravenous use), Yervoy® (ipilimumab injection for intravenous use); AND
B) The patient has life-threatening myocarditis, pericarditis, arrhythmias, or impaired ventricular function according to the prescriber; AND
C) The 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.[1]

Limited dosing information is available. FDA-approved doses up to 15 mg/kg are recommended for the management of acute rejection in renal transplantation.

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5. 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.[17-20]

Limited dosing information is available. FDA-approved doses up to 15 mg/kg are recommended for the management of acute rejection in renal transplantation.

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6. Graft-vs.-Host Disease. Approve for 1 month if the patient meets the following criteria (A, B, and C):
A) The patient has acute disease; AND
B) The patient's disease is refractory to 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.[26-29]

Limited dosing information is available. FDA-approved doses up to 15 mg/kg are recommended for the management of acute rejection in renal transplantation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Atgam has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

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

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	12/04/2019