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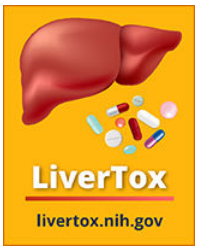

Antithymocyte Globulin

Updated: July 25, 2017.

OVERVIEW

Introduction

Antithymocyte globulin (ATG) is an antibody preparation derived from rabbits or horses hyperimmunized with human thymocytes, which is used to prevent or treat acute cellular rejection after solid organ transplantation and as a therapy of acute aplastic anemia. ATG has been linked to acute elevations in serum enzyme elevations shortly following infusions, but has not been linked to cases of clinically apparent liver injury. ATG is a potent immunosuppressive agent and may result in reactivation of hepatitis B in susceptible patients.

Background

Antithymocyte globulin is a hyperimmune globulin preparation made from plasma of rabbits or horses that have been immunized with human thymocytes or T cells. ATG is given by infusion only and leads to a rapid decrease in circulating T cells. ATG has been shown to be effective in preventing and treating acute cellular rejection after renal transplantation, and has been used extensively for the same indications after heart and liver transplantation. The antibodies are polyclonal and are directed at multiple T cell markers (such as CD2, CD3, CD4, CD8, CD 11) as well as HLA markers, beta-2-microglobulin and other tissue antigens (including cytoplasmic and nuclear liver antigens). Equine ATG is also used to treat severe aplastic anemia. ATG was initially approved for use in the United States as treatment of acute cellular rejection after renal transplantation. Since then, the indications for its use have been broadened, although there remains considerable off label use as well. Two commercial products are available in the United States: Thymoglobulin (rabbit ATG) and Atgam (horse ATG). Dose regimens vary by product and clinical indications. The usual regimen for treating acute rejection in adults is a 7 to 14 day course of daily infusion of 1.5 mg/kg of Thymoglobulin or 15 mg/kg of Atgam. ATG is typically used in combination with other immunosuppressive agents and should be prescribed only by physicians experienced in management of immunosuppression. Adverse events are common during ATG administration, but many are due to the underlying condition and other complications of organ transplantation or aplastic anemia. Because ATG is made from animal serum, it can induce serious immune mediated reactions such as acute infusion reactions, anaphylaxis, serum sickness and cytokine release syndrome. ATG is a foreign protein (xenotypic) and may induce inactivating antibodies with repeated use. Furthermore, the initial engagement of T cells by the antibody can result in a transient, acute release of proinflammatory cytokines (cytokine release syndrome) with symptoms of high fever, weakness, dyspnea, nausea, chest pain and diarrhea arising within the first two days of starting therapy. Less common, but potentially severe adverse reactions reported to occur after ATG therapy include bacterial and opportunistic infections, reactivation of viral infections (EBV, HSV, CMV, HBV, RSV, among others), acute thromboses, and malignancies, particularly EBV-associated lymphoproliferative disorders.

Hepatotoxicity

When given as a part of induction therapy for solid organ transplantation, ATG has not been linked to serum enzyme elevations or hepatotoxicity, but it is given with other medications and in preparation for major surgery so that some degree of liver injury might well be missed. In patients with aplastic anemia given ATG, transient serum enzyme elevations arising a few days after the infusions have been reported to occur in up to one-third of patients. These abnormalities generally resolve spontaneously without jaundice or symptoms. Serum alkaline phosphatase and bilirubin levels rise minimally, if at all. There have been no convincing cases of acute, clinically apparent liver injury caused by ATG infusions. Indeed, administration of ATG for acute rejection after liver transplantation is usually followed by a prompt decrease in serum enzymes and jaundice, and administration of ATG for aplastic anemia with hepatitis or hepatitis from check point inhibitors such as ipilumumab commonly results in a prompt improvement in the jaundice and serum enzyme elevations. ATG has occasionally been implicated in causing a worsening of chronic hepatitis C after transplantation, but is not generally implicated as a major cause of long term severe outcomes of recurrent hepatitis C infection.

Likelihood score: E* (unproven, but suspected cause of anicteric liver injury).

ATG is a potent immunosuppressive agent and may be capable of causing reactivation of chronic hepatitis B. However, when used in prevention of organ rejection it has not been linked to cases of reactivation, perhaps because patients at risk are routinely given prophylaxis and the role of ATG versus other rejection medications (cyclosporine, tacrolimus, corticosteroids) is not clear.

Mechanism of Injury

The cause of serum enzyme elevations after ATG use is not known, but may relate to cytotoxicity of the polyclonal antibodies to liver cells or to the known propensity of injured, apoptotic T lymphocytes to home to the liver. Liver injury generally arises after ATG infusions have stopped or between courses of treatment.

Outcome and Management

The liver injury associated with ATG therapy is generally mild and self-limited without symptoms or jaundice. The other forms of hypersensitivity reactions to ATG are usually more likely to call for alteration in administration or avoidance of further infusions.

Monoclonal agents used in the treatment or prevention of transplant rejection include alemtuzumab, basiliximab, daclizumab, and muromonab.

Drug Class: Transplant Agents, Polyclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Antithymocyte Globulin [Equine] – Atgam®

Antithymocyte Globulin [Rabbit] – Thymoglobulin®

DRUG CLASS

Transplant Agents

COMPLETE LABELING

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Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Antithymocyte [Antilymphocyte] Globulin	308067-60-9	Polyclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 25 July 2017

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

(Review of hepatotoxicity of immunosuppressive agents mentions ATG and problems of reactivation of hepatitis).

Krensky AM, Bennett WM, Vincenti F. Immunosuppressants, tolerogens, and immunostimulants. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1005-1029.

(Textbook of pharmacology and therapeutics).

Starzl TE, Marchioro TL, Hutchinson DE, Porter KA, Cerilli GJ, Brettschneider L. The clinical use of antilymphocyte globulin in renal homotransplantation. Transplantation 1967; 5: Suppl: 1100-5. PubMed PMID: 4167452.

(Among 20 renal transplant recipients treated with antilymphocyte globulin [horse], 19 survived and had good renal function after 1-7 months; no mention of ALT elevations or hepatotoxicity).

Najarian JS, Simmons RL. The clinical use of antilymphocyte globulin. N Engl J Med 1971; 285: 158-66. PubMed PMID: 4103453.

(Review of the history of development, mechanism of action, efficacy and side effects of antilymphocyte globulin; no mention of ALT elevations or hepatotoxicity).

Doney KC, Weiden PL, Buckner CD, Storb R, Thomas ED. Treatment of severe aplastic anemia using antithymocyte globulin with or without an infusion of HLA haploidentical marrow. Exp Hematol 1981; 9: 829-34. PubMed PMID: 7035206.

(Among 19 patients with aplastic anemia treated with ATG with or without marrow infusions, survival was 42% and side effects included fever and chills in all, rash in 84%, liver enzyme elevations in 37% with serum sickness symptoms responding to corticosteroid therapy).

Harada M, Gale RP. Evaluation of antithymocyte globulin for human bone marrow transplantation. Antihematopoietic and immunosuppressive activity. Transplantation 1982; 33: 625-30. PubMed PMID: 7048664.

(Absorption of ATG using fetal liver cells was effective in removing cytotoxicity to hematopoietic stem cells, but did not affect the immunosuppressive activity [which is directed primarily against mature T cells] of the antibody preparation).

Champlin R, Ho W, Gale RP. Antithymocyte globulin treatment in patients with aplastic anemia: a prospective randomized trial. N Engl J Med 1983; 308: 113-8. PubMed PMID: 6336819.

(Controlled trial in 42 patients with severe aplastic anemia found response rate of 52% with ATG vs 0% with placebo; all ATG recipients had symptoms of serum sickness responding to corticosteroids; no mention of ALT elevations or hepatotoxicity).

Greco B, Bielory L, Stephany D, Hsu SM, Gascon P, Nienhuis A, Young N. Antithymocyte globulin reacts with many normal human cell types. Blood 1983; 62:1047-54. PubMed PMID: 6354303.

(ATG has antibody reactivity not just to T cells, but also to granulocytes, bone marrow cells, and yields nuclear and cytoplasmic staining of many tissues including hepatocytes).

Doney K, Storb R, Buckner CD, McGuffin R, Witherspoon R, Deeg HJ, Appelbaum FR, et al. Treatment of aplastic anemia with antithymocyte globulin, high-dose corticosteroids, and androgens. Exp Hematol 1987; 15: 239-42. PubMed PMID: 3493172.

(Among 46 patients with aplastic anemia treated with ATG, corticosteroids and androgens, long term survival was 74%; side effects included serum sickness in 23 [50%] and ALT elevations in 12 [26%], which led to discontinuation of androgens in 8 [17%]).

Means RT Jr, Krantz SB, Dessypris EN, Lukens JN, Niblack GD, Greer JP, Flexner JM, et al. Re-treatment of aplastic anemia with antithymocyte globulin or antilymphocyte serum. Am J Med 1988; 84: 678-82. PubMed PMID: 3261125.

(Among 22 patients with aplastic anemia treated with ALS or ATG, 32% responded to the initial course and 44% [4 of 9] to retreatment; no mention of side effects).

Claesson K, Tufveson G, Wahlberg J. Treatment with poly- and monoclonal antilymphocyte antibodies: assessment of efficacy and safety in transplantation. Transplant Proc 1992; 24: 314. PubMed PMID: 1539293.

(Among 145 patients undergoing organ transplantation, graft survival and adverse events were similar in those who received antibody therapy of rejection and those who did not; no mention of ALT elevations or hepatotoxicity).

Toren A, Ilan Y, Or R, Kapelushnik J, Nagler A. Impaired liver function tests in patients treated with antithymocyte globulin: implication for liver transplantation. Med Oncol 1997; 14: 125-9. PubMed PMID: 9468033.

(Among 16 patients receiving ATG in preparation of hematopoietic cell transplantation, serum ALT, AST, GGT and LDH levels increased by 1 to 5 fold [ALT rising from 52 to 185 U/L by day 3 and bilirubin from 1.1 to 1.9 mg/dL], but not in 5 patients with aplastic anemia treated with ATG).

Killick SB, Marsh JC, Booth JC, Gordon-Smith EC. Liver function abnormality following treatment with antithymocyte globulin for aplastic anaemia. Bone Marrow Transplant 1997; 19: 249-51. PubMed PMID: 9028554.

(Among 18 patients with aplastic anemia treated with ATG [horse and rabbit] in 1-3 courses of 5 daily injections, 15 had a transient rise in ALT [peak 49-741 U/L] with no change in bilirubin or Alk P, usually rising within 4 days after the infusions and persisting for several weeks, but in 2 patients for more than 30 days).

Brown KE, Tisdale J, Barrett AJ, Dunbar CE, Young NS. Hepatitis-associated aplastic anemia. N Engl J Med 1997; 336: 1059-64. PubMed PMID: 9091802.

(Among 10 patients with severe aplastic anemia arising 1-7 weeks after onset of acute seronegative hepatitis who were treated with horse ATG [4 days] and cyclosporine [6 months], the long term response rate was 70%, and ALT levels fell in all 10 patients, becoming normal within 30 days in 9).

Marsh J, Schrezenmeier H, Marin P, Ilhan O, Ljungman P, McCann S, Socie G, et al. Prospective randomized multicenter study comparing cyclosporin alone versus the combination of antithymocyte globulin and

cyclosporin for treatment of patients with nonsevere aplastic anemia: a report from the European Blood and Marrow Transplant (EBMT) Severe Aplastic Anaemia Working Party. Blood 1999; 93: 2191-5. PubMed PMID: 10090926.

(Among 115 patients with aplastic anemia treated with cyclosporine alone or in combination with ATG [horse], overall response rates were higher with the combination; no discussion of side effects).

Frickhofen N, Rosenfeld SJ. Immunosuppressive treatment of aplastic anemia with antithymocyte globulin and cyclosporine. Semin Hematol 2000; 37: 56-68. PubMed PMID: 10676911.

(Review of the therapy of aplastic anemia focusing upon ATG and cyclosporine).

Midtvedt K, Fauchald P, Lien B, Hartmann A, Albrechtsen D, Bjerkely BL, Leivestad T, et al. Individualized T cell monitored administration of ATG versus OKT3 in steroid-resistant kidney graft rejection. Clin Transplant 2003; 17: 69-74. PubMed PMID: 12588325.

(Among 55 patients undergoing renal transplantation treated with variable doses of either ATG or muromonab based upon T cell counts, rejection rates were similar as were adverse events; no mention of ALT elevations or hepatotoxicity).

Champlin RE, Perez WS, Passweg JR, Klein JP, Camitta BM, Gluckman E, Bredeson CN, et al. Bone marrow transplantation for severe aplastic anemia: a randomized controlled study of conditioning regimens. Blood 2007; 109: 4582-5. PubMed PMID: 17272503.

(Among 134 patients undergoing hematopoietic cell transplantation for aplastic anemia treated with cyclophosphamide alone or in combination with ATG, rates of bone marrow recovery and graft-vs-host disease were similar in the two groups, as were side effects of infection; no mention of ALT elevations or hepatotoxicity).

Lundquist AL, Chari RS, Wood JH, Miller GG, Schaefer HM, Raiford DS, Wright KJ, et al. Serum sickness following rabbit antithymocyte-globulin induction in a liver transplant recipient: case report and literature review. Liver Transpl 2007; 13: 647-50. PubMed PMID: 17377915.

(45 year old woman received ATG for 4 days at the time of liver transplantation for hepatitis C and developed fever 9 days after transplant, followed by arthralgias diagnosed as serum sickness; no mention of liver tests).

Boillot O, Seket B, Dumortier J, Pittau G, Boucaud C, Bouffard Y, Scoazec JY. Thymoglobulin induction in liver transplant recipients with a tacrolimus, mycophenolate mofetil, and steroid immunosuppressive regimen: a five-year randomized prospective study. Liver Transpl 2009; 15: 1426-34. PubMed PMID: 19877264.

(Among 93 patients undergoing liver transplantation with or without ATG induction, rates of acute rejection, graft and patient survival were similar; no mention of hepatotoxicity).

Atta EH, Dias DS, Marra VL, de Azevedo AM. Comparison between horse and rabbit antithymocyte globulin as first-line treatment for patients with severe aplastic anemia: a single-center retrospective study. Ann Hematol 2010; 89: 851-9. PubMed PMID: 20373101.

(Retrospective analysis of ATG treatment of 71 patients with aplastic anemia, found 6 month response rates higher with horse [60%] compared to rabbit [35%] ATG; no mention of ALT elevations or hepatotoxicity).

Schmitt TM, Phillips M, Sawyer RG, Northup P, Hagspiel KD, Pruett TL, Bonatti HJ. Anti-thymocyte globulin for the treatment of acute cellular rejection following liver transplantation. Dig Dis Sci 2010; 55: 3224-34. PubMed PMID: 20238251.

(Results of treating 20 patients with ATG for acute rejection after liver transplantation; all responded with improvements in ALT and AST, but those with hepatitis C had recurrence of injury and one patient died after a marked ALT elevation following therapy).

Cai J, Terasaki PI. Induction immunosuppression improves long-term graft and patient outcome in organ transplantation: an analysis of United Network for Organ Sharing registry data. Transplantation 2010; 90: 1511-5. PubMed PMID: 21057388.

(Since 2003, most solid organ transplant recipients have received induction therapy, and analyses of the UNOS registry for this period shows highest rates of patient and graft survival with alemtuzumab [89% 5 year patient survival] as compared to ATG [89%], basiliximab [84%], daclizumab [77%], steroids [75%] or no induction [71%]).

Marks WH, Ilsley JN, Dharnidharka VR. Posttransplantation lymphoproliferative disorder in kidney and heart transplant recipients receiving thymoglobulin: a systematic review. Transplant Proc 2011; 43: 1395-404. PubMed PMID: 21693205.

(Systematic review of PTLD after induction therapy with ATG before transplantation found overall rate of 1% with higher rates in patients not given prophylaxis with antiviral agents).

Scheinberg P, Nunez O, Weinstein B, Scheinberg P, Biancotto A, Wu CO, Young NS. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N Engl J Med 2011; 365: 430-8. PubMed PMID: 21812672.

(Controlled trial of different ATG products in 120 patients with severe aplastic anemia found higher rates of response to the horse vs rabbit ATG [68% vs 37% at 6 months], but similar profile of side effects, the major serious side effects being infection; no mention of ALT elevations or hepatotoxicity).

Ahmed T, Pandey R, Shah B, Black J. Resolution of ipilimumab induced severe hepatotoxicity with triple immunosuppressants therapy. BMJ Case Rep 2015; 1-4. PubMed PMID: 26174726.

(50 year old woman with melanoma developed fatigue and fever during ipilumumab therapy of melanoma [bilirubin 0.9 mg/Dl, ALT 640 U/L, Alk P 366 U/L], resolving within 30 days of starting methylprednisone and horse ATG).

Chmiel KD, Suan D, Liddle C, Nankivell B, Ibrahim R, Bautista C, Thompson J, et al. Resolution of severe ipilimumab-induced hepatitis after antithymocyte globulin therapy. J Clin Oncol 2011; 29: e237-40. PubMed PMID: 21220617.

(60 year old man with melanoma developed anorexia, rash and fever 10 days after a second infusion of ipilimumab [peak bilirubin 1.2 mg/dL, ALT 2521 U/L, Alk P 275 U/L] treated with methyl prednisolone and relapsed when it was tapered [bilirubin 3.9 mg/dL, ALT 6362 U/L, Alk P 147 U/L, INR 1.4], with rapid recovery [2-3 weeks] upon increasing corticosteroids and administering 4 infusions of rabbit ATG).

Chang A, Lee-Lam FY, Wang J, Cheng YH. Transient liver function abnormality following treatment with rabbit antithymocyte globulin for nonmyeloablative hematopoetic stem cell transplant: two case reports. J Oncol Pharm Pract 2015; 21: 67-71. PubMed PMID: 24395543.

(Two patients, 66 and 72 year old women with leukemia and lymphoma developed ALT elevations [peak 702 and 689 U/L] within a few hours of finishing 5-day infusions of rabbit ATG which resolved within one week; patients also received acetaminophen and methyl prednisolone).

Scheinberg P, Nunez O, Weinstein B, Scheinberg P, Wu CO, Young NS. Activity of alemtuzumab monotherapy in treatment-naive, relapsed, and refractory severe acquired aplastic anemia. Blood 2012; 119: 345-54. PubMed PMID: 22067384.

(In three prospective studies evaluating alemtuzumab [monoclonal anti-CD52] in a total of 90 patients, response rates were lower than with ATG in treatment-naïve patients, but alemtuzumab may have a role in ATG refractory and relapsed patients; no mention of ALT elevations or hepatotoxicity in summary of adverse reactions).

Mangus RS, Fridell JA, Vianna RM, Kwo PY, Chen J, Tector AJ. Immunosuppression induction with rabbit anti-thymocyte globulin with or without rituximab in 1000 liver transplant patients with long-term follow-up. Liver Transpl 2012; 18: 786-95. PubMed PMID: 22237953.

(Description of results using ATG induction in 1013 patients underlying liver transplantation at a single referral center; no mention of hepatotoxicity or ALT elevations).

Berenguer M, Pons JA. Rabbit anti-thymocyte globulin in liver transplantation: all that glitters is not gold, but 1000 patients are so many to dazzle. Liver Transpl 2012; 18: 755-60. PubMed PMID: 22431230.

(Editorial in response to Magnus [2012] decrying the lack of prospectively controlled trials of induction regimens before transplantation).

Kadia TM, Borthakur G, Garcia-Manero G, Faderl S, Jabbour E, Estrov Z, York S, et al. Final results of the phase II study of rabbit anti-thymocyte globulin, ciclosporin, methylprednisone, and granulocyte colony-stimulating factor in patients with aplastic anaemia and myelodysplastic syndrome. Br J Haematol 2012; 157: 312-20. PubMed PMID: 22360602.

(Open label trial of ATG [rabbit] with cyclosporine, corticosteroids and GCSF in 24 patients with aplastic anemia and 24 with myelodysplasia reported common side effects were neutropenia [50%], infusion reactions [27%], serious infections [27%], increased ALT levels [33%], and elevations in bilirubin levels [31%]).

Taylor S, Hu C, Pan DH, Manwani D. Treatment of acquired aplastic anemia in patients with acute liver failure occurring concurrently: a case series. J Pediatr Hematol Oncol 2012; 34: e349-52. PubMed PMID: 23018574.

(Two patients with aplastic anemia and severe hepatitis were treated with ATG, corticosteroids and cyclosporine [amounts and regimens not given], both patients recovering and liver injury resolving despite the immunosuppressive therapy).

Ecsedi M, Schmohl J, Zeiser R, Drexler B, Halter J, Medinger M, Duyster J, et al. Anti-thymocyte globulin-induced hyperbilirubinemia in patients with myelofibrosis undergoing allogeneic hematopoietic cell transplantation. Ann Hematol 2016; 95: 1627-36. PubMed PMID: 27480090.

(Retrospective analysis of 94 patients with myelofibrosis (MF) and 158 with other conditions undergoing hematopoietic cell transplantation with conditioning regimens including ATG, found that 90% of MF vs 54% of others developed bilirubin elevations after ATG infusions, rising from 0.6-1.5 to 1.0-4.6 mg/dL and rapidly returning to baseline, inconsistently associated with serum enzyme; no mention of direct bilirubin or bile acid levels).

Lee JG, Lee J, Lee JJ, Song SH, Ju MK, Choi GH, Kim MS, et al. Efficacy of rabbit anti-thymocyte globulin for steroid-resistant acute rejection after liver transplantation. Medicine (Baltimore) 2016; 95: e3711. PubMed PMID: 27281070.

(Retrospective analysis of 11 cases of steroid-resistant acute cellular rejection treated with rabbit ATG for 6-10 days found that all responded with prompt decline in bilirubin [mean 6.5 to 4.8 mg/dL], ALT [327 to 70 U/L] and Alk P [359 to 299 U/L], and most had normal values by 2 weeks).

Petite SE, Bollinger JE, Eghtesad B. Antithymocyte globulin induction therapy in liver transplant: old drug, new uses. Ann Pharmacother 2016; 50: 592-8. PubMed PMID: 27147705.

(Review of the use of rabbit ATG in induction regimens for liver transplantation; no mention of hepatotoxicity).