Antithymocyte Globulin (ATG) Dosing and Controversies

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Disclosure

- I have no actual or potential conflicts of interest

Objectives

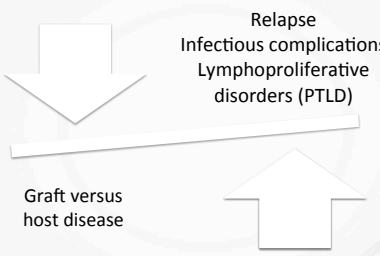
- Describe antithymocyte globulin (ATG) dosing regimens and strategies in hematopoietic cell transplantation (HCT).
- Evaluate the role of ATG in HCT based on stem cell source and type of preparative regimen.
- Outline strategies for the management of positive ATG test dose reactions and apply to a patient receiving horse ATG for aplastic anemia.

Antithymocyte Globulin

- Polyclonal antibodies purified from horse or rabbit serum
- Primary mechanism: *in vivo* depletion of T-lymphocytes in the blood, spleen and lymph nodes
  - Native recipient T cells
  - Donor infused T cells
- Effects on B cells, dendritic cells, NK cells
- Tolerance induction
  - Expansion and generation of T regulatory cells

Leukemia. 2007;21:1387-94

Antithymocyte globulin: A Balancing Act



Antithymocyte globulin

- Product preparation, dose, and schedule impact the extent and specificity of T-cell depletion and immune reconstitution
- Different preparations should be regarded as unique drugs

ATG	Manufacturer	Host Animal	Immunized With	Comments
Atgam	Pharmacia Upjohn	horse	human thymocytes	FDA approved in US
Thymoglobulin	Genzyme	rabbit	human thymocytes	FDA approved in US
Lymphoglobulin	Genzyme	horse	human thymocytes	No longer available
ATG-Fresenius	Fresenius	rabbit	human jurkat cell line	Not available/FDA approved in US

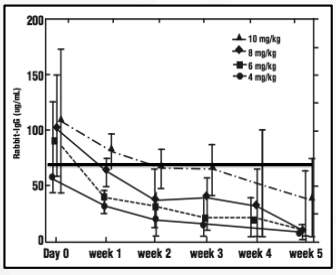
Why are we still asking this question?

- Differences in ATG preparation, dose, schedule
  - Cannot extrapolate results from one agent to another
- Very few adequately powered, prospective, randomized studies
- MANY small, single center, retrospective, non-randomized trials with heterogeneous patient populations
- Evolving trends in HCT
  - Increase in reduced intensity conditioning, cord blood transplant, haploidentical transplant
  - Older patient demographic

What is the ideal dose and timing of ATG?

ATG Pharmacokinetics

Rabbit IgG Levels, n = 61 (mean ± 95% CI)



- Total ATG administered in 2mg/kg doses, last dose on day -1
- Wide interpatient variation in IgG levels
- Lower risk of grade 2-4 aGVHD at rATG levels > 70mcg/mL on day 0 vs levels < 70mcg/mL (11% vs 48%, p<0.01)

Haematologica. 2005;90:931-38

rATG Dosing

- Retrospective, dose-finding study (n = 162)
- Hematologic malignancies, unrelated donors
- Conditioning: Cy-TBI or BuCy
- GVHD prophylaxis: cyclosporine + methotrexate
- Comparator groups: rATG (Thymoglobulin)
  - 4mg/kg (n=51), 6mg/kg (n=37), 8mg/kg (n=19), 10mg/kg (n=55)
  - Dosing: 2mg/kg/day, last administration = day -1

Transplantation. 2004;78:122-27.

rATG Dosing

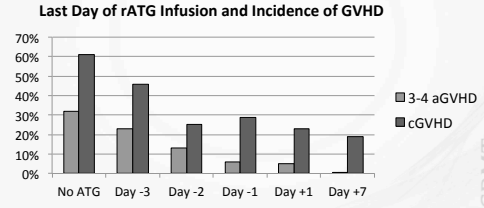
Event	HR (95% CI)	P-value
2-4 aGVHD ATG 4mg/kg	2.7 (1.2-5.9)	0.015
3-4 aGVHD ATG 4mg/kg	4.1 (1.1-15)	0.03
Death from infection ATG 10mg/kg	Not reported	0.09
TRM ATG 6-8 mg/kg	0.35 (0.13-0.94)	0.03
Death ATG 6-8 mg/kg	0.45 (0.22-0.9)	0.03

- Multivariate analysis
- Intermediate dose range favored to decrease GVHD, TRM and death

Transplantation. 2004;78:122-27.

rATG Timing

- Timing of rATG (Thymoglobulin) in unrelated/mis-matched related donor HCT (n = 257)
- Total dose of rATG not reported



Blood. 2003;102:242a: Abstract 851

ATG Dosing and Timing: Conclusions

- Large interpatient variability in ATG PK parameters
  - Long half-life
  - Present in serum for up to 5 weeks
- ATG levels pre-HCT correlate with risk of developing GVHD
  - Research application for individualized dosing
- Dose-response relationship of ATG's effect on GVHD and infection, favoring an intermediate dose range
- Timing of ATG is significant
  - Lower doses may be given closer to day zero, higher doses may be given early in conditioning

Should ATG be used in myeloablative conditioning?

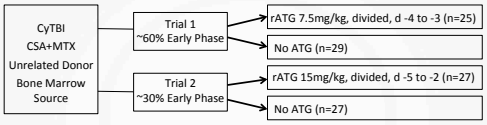
Audience Poll

At your institution, ATG is used as part of the standard preparative regimen in which patient population(s):

A. Both myeloablative related and unrelated donors
B. Only myeloablative related donors
C. Only myeloablative unrelated donors
D. We do not use ATG as a standard component of the preparative regimen
E. Attending preference

ATG in Unrelated Donors: GITMO Study

- Prospective, randomized, multicenter (1995-2000)



	Trial 1			Trial 2		
	No ATG	rATG 7.5mg/kg	P-value	No ATG	rATG 15mg/kg	P-value
3-4 aGVHD	9 (36%)	12 (41%)	0.8	**14 (50%)**	**3 (11%)**	**<0.01**
TRM	39%	43%	0.7	62%	49%	0.9
Relapse	12%	10%	0.6	18%	36%	0.8
OS	155%	56%	0.8	43%	32%	0.8

Cy: cyclophosphamide, TBI: total body irradiation, CSA: cyclosporine, MTX: methotrexate, rATG: rabbit ATG (Thymoglobulin), TRM: treatment related mortality, OS: overall survival

Blood. 2001;98:2942-2947 / *Biol Blood Marrow Transplant*. 2006;12:560-65

ATG in Unrelated Donors: GITMO Study

- Long term follow-up reported in 2006
  - Patients surviving >100 days included (n=75)
  - Outcomes at a median follow-up of 5.7 years

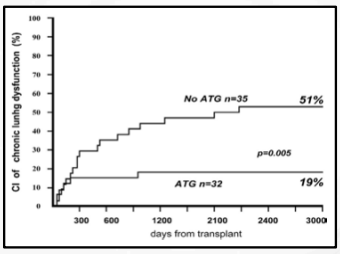
	No ATG (n = 37)	rATG (n = 38)	P-value
cGVHD	60%	37%	0.05
Extensive cGVHD	41%	15%	0.01
Chronic Lung Dysfunction	51%	19%	<0.01
Karnofsky ≥ 90%	57%	89%	0.03

- No significant differences in TRM, OS, relapse
- Limitations: Study performed in the 1990s, 2 different ATG doses used, possibility of MMUD

Blood. 2001;98:2942-2947 / *Biol Blood Marrow Transplant*. 2006;12:560-65

ATG in Unrelated Donors: GITMO Study

- Cumulative incidence of chronic lung dysfunction



Blood. 2001;98:2942-2947 / *Biol Blood Marrow Transplant*. 2006;12:560-65

ATG in Unrelated Donors: ATG-F Study

- Prospective, randomized, multicenter (2003-2007)
- Treatment arms:
  - CSA + MTX (n = 98)
  - CSA + MTX + ATG-F 60mg/kg, divided, d -3 to -1 (n = 103)
- Hematologic malignancies
- Majority PBSC source
- 56% advanced disease in no ATG vs. 38% in ATG-F arm

Lancet Oncol. 2009;10:855-64

ATG in Unrelated Donors: ATG-F Study

	No ATG (n = 37)	ATG-F (n = 38)	HR (95% CI)	P-value
3-4 aGVHD	24.5%	12%	0.5 (0.25-1.01)	0.054
cGVHD @ 2y	59%	31%	0.3 (0.21-0.55)	<0.01
Extensive cGVHD @ 2y	43%	12%	0.2 (0.11-0.43)	<0.01
Extensive cGVHD @ 3y	45%	12%	0.2 (0.1-0.39)	<0.01
Survival free of immunosuppressive therapy @3y	17%	53%	not reported	<0.01

- No significant differences in TRM, OS, relapse

Lancet Oncol. 2009;10:855-64 / *Blood.* 2011;117:6375-82

ATG in Matched Related Donors

- No recent, prospective, multicenter, randomized trials

	Disease Status	Source	ATG	GVHD	Outcomes
Russel 2007 n = 108	Hematologic malignancies High risk: 26%	PBSC	No ATG vs rATG 4.5mg/kg	aGHVD: NS **cGVHD: 96 vs 55% (p <0.01)**	NRM @ 100d: 17 vs 4% (p <0.01), @ 4y: 34 vs 9% (p <0.02) Relapse: 22 vs 43% (p 0.05) OS: 50 vs 66% (p 0.05)
Kroger 2002 n = 102	Good risk myeloid leukemias	Mostly BM	No ATG vs ATG-F 30-120mg/kg	3-4 aGVHD: 32 vs 7% (p <0.01) **cGVHD: 67 vs 36% (p <0.01)**	NRM, relapse, OS: NS

PBSC: peripheral blood stem cell, rATG: rabbit ATG (Thymoglobulin), NS: not significant, NRM: non-relapse mortality, OS: overall survival, BM: bone marrow, ATG-F: ATG-Fresenius

*Biol Blood Marrow Transplant.*2007;13:299-306 / *Bone Marrow Transplant.* 2002;29:683-89

ATG and Quality of Life

- Prospective, open label, single-center trial (n = 96)
  - Cytarabine, cyclophosphamide, busulfan, simustime +/- ATG-F 16mg/kg, divided, days -4 to -1
  - GVHD prophylaxis: CSA+MTX
  - Peripheral blood source, 77% sibling donor
- Validated QoL instruments
  - Karnofsky Performance Scale (KPS)
  - European Organization for Research and Treatment Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30)

Biol Blood Marrow Transplant. 2012;18:593-99

ATG and Quality of Life

- HCT Outcomes
  - ATG-F group had significantly lower rates of aGVHD (overall and grade 3-4) and cGVHD, increased rates of infection
  - No difference between groups for relapse or survival
- QoL Outcomes (final assessment 1 year post HCT)
  - KPS: 70% of patients in ATG-F group vs 29% in no ATG group had KPS scores ≥ 80 (carry on normal activity, work)
  - EORTC QLQ-C30: Statistically significant increased scores in global QoL and decreased fatigue in ATG-F group

Biol Blood Marrow Transplant. 2012;18:593-99

ATG in Myeloablative HCT: Conclusions

- ATG reduces chronic GVHD
- Reduction of GVHD does not translate into an increase in relapse or a survival advantage
  - Limited data in high risk disease patients
  - Would the reduction in cGVHD translate into a survival advantage long term?
- Quality of life may be improved in patients receiving ATG due to reduced GVHD
- Outcomes with ATG related to source of stem cells (bone marrow vs. peripheral blood) is largely untested

Audience Response Question #1

In myeloablative HCT, the use of ATG has demonstrated consistent benefits in:

A. Reduction of acute GVHD
B. Reduction of chronic GVHD
C. Reduction of treatment related mortality
D. Improved overall survival
E. All of the above

Should ATG be used in reduced intensity conditioning?

Reduced Intensity Conditioning

- Reduction in early transplant related mortality allowing patients who are otherwise ineligible for myeloablative conditioning to undergo HCT
- Increase in the use of RIC over the last decade
- Outcomes rely on the integrity of a graft-versus-tumor effect
- Immune manipulations that might weaken allo-immunity may compromise transplant outcomes

ATG in Reduced Intensity Conditioning

	Disease	ATG	Donor	GVHD	Outcomes
Malard 2011 Retro n = 68	37% CR, 45% PR, 18% PD	**no ATG vs rATG 5mg/kg**	57% MRD, 38% MUD, 4% MMRD/UD	**3-4 aGVHD: 44 vs 15% (p <0.01) ecGVHD: 58 vs. 12% (p <0.01)**	2y TRM: NS 2y OS: NS 2y PFS: NS
Crocchiolo 2013 Retro n = 229	~25% high risk	**rATG LD: 2.5mg/kg HD: 5mg/kg**	LD: 98% MRD HD: 62% MRD	**2-4 aGHVD: 42 vs 23% (p <0.01) 3-4 aGVHD: 23 vs 10% (p 0.03) ecGVHD: 69 vs 35% (p < 0.01)**	3y OS: NS Relapse: NS
Hamadani 2009 Retro n = 72	LD: 94% high risk HD: 72% high risk	**rATG LD: 6mg/kg HD: 7.5mg/kg**	~90% MUD	2-4 aGVHD: NS cGVHD: NS	**CMV: 30 vs 64% (p <0.01) Bacterial infections: 18 vs. 56% (p <0.01) 1y NRM: 3 vs 18% (p 0.03) 1y OS: 84 vs 64% (p 0.07)** 2y Relapse: NS

CR: complete response, PR: partial response, PD: progressive disease, rATG: rabbit ATG (Thymoglobulin), ec: extensive chronic TRM: treatment related mortality, OS: overall survival, PFS: progression free survival, LD: low dose, HD: high dose, NRM: non-relapse mortality

Biol Blood Marrow Transplant. 2009;15:1422-30 / *Cancer*. 2013;119:986-92 / *Biol Blood Marrow Transplant*. 2011;17:1698-1703

RIC: CIBMTR Study

- Retrospective registry analysis of adult patients with hematologic malignancies who received RIC HCT between 2000 – 2007
- Treatment Groups
  - T cell-replete (n = 879)
  - ATG (n = 584)
  - Alemtuzumab (n = 213)
- Outcomes: aGVHD, cGVHD, relapse, non-relapse mortality, disease free survival, and overall survival

Blood. 2011;117:6963-70

	ATG, no. (%)	T cell-replete, no. (%)	P-value
No. of patients	584	879	
ATG preparation			
rATG (median 7 mg/kg)	405 (70)		
hATG (median 40 mg/kg)	160 (27)		
Not reported	19 (3)		
Disease status before HCT			
Early	193 (33)	271 (31)	NS
Advanced	391 (67)	608 (69)	
Conditioning regimen			
BuFlu	375 (54)	300 (34)	<0.001
MelFlu	132 (23)	310 (35)	
CyFlu	77 (13)	269 (31)	
Graft type			
Bone marrow	84 (14)	83 (9)	0.001
Peripheral blood	500 (86)	796 (91)	
Donor type			
HLA-matched sibling	228 (39)	517 (59)	<0.001
Unrelated, 8/8	251 (43)	278 (32)	
Unrelated, 7/8	105 (18)	84 (10)	

rATG: rabbit ATG (Thymoglobulin), hATG: horse ATG, Bu: busulfan, Flu: fludarabine, Mel: melphalan, Cy: cyclophosphamide, HLA: human leukocyte antigen

Blood. 2011;117:6963-70

CIBMTR Study: Multivariate Analysis

Outcome	ATG	T cell-replete	HR (95% CI)	P-value
Grade 2-4 aGVHD	38%	40%	0.88 (0.74-1.04)	0.12
Grade 3-4 aGVHD	21%	22%	0.86 (0.69-1.08)	0.19
cGVHD	40%	52%	0.69 (0.59-0.81)	<0.01
Relapse	49%	38%	1.53 (1.29-1.81)	<0.01
Non-relapse mortality	26%	23%	1.34 (1.07-1.67)	0.01
Disease free survival	25%	39%	Not reported	<0.01
Overall survival	38%	46%	Not reported	<0.01

- EBV-PTLD: 2 pts (T cell-replete) vs. 12 pts (ATG, 4 deaths)
- ATG was associated with inferior DFS regardless of preparation and dose administered (timing not reported)

Blood. 2011;117:6963-70

CIBMTR Study Conclusions

- Limitations
  - Non-randomized trial design
  - Heterogeneous ATG source, dose, schedule
  - Limited information on infectious complications
  - Limited data on immune reconstitution and DLI
- Conclusions
  - ATG is associated with a lower risk of cGVHD but an increased risk of relapse and inferior OS in RIC HCT

Blood. 2011;117:6963-70

ATG in Reduced Intensity Conditioning: Conclusions

- ATG may reduce GVHD in patients with hematologic malignancies undergoing RIC for allo-HCT
- Low doses (≤ 2.5mg/kg) do not have adequate GVHD lowering and higher doses (> 7mg/kg) are associated with an increased risk of infection, relapse, and potentially mortality
- RCTs comparing intermediate-dose ATG vs. T cell-replete regimens in RIC HCT are needed
- Minimize use of ATG in RIC HCT to patients at higher risk of GVHD and those with lower risk of relapse

Should ATG be used in umbilical cord blood transplant?

Umbilical Cord Blood Transplant

- UCBT has expanded the donor pool for patients who do not have an HLA-matched sibling or unrelated donor
- Less stringent HLA matching criteria resulting in similar outcomes to matched unrelated donor HCT
- Outcomes are limited by increased treatment related mortality
  - Graft versus host disease
  - Engraftment
  - Opportunistic infections
  - Immune reconstitution

How does ATG alter these endpoints?

Risk factors for GVHD after UCBT

- University of Minnesota database of 265 patients (>10 years) undergoing single or double UCBT (1994-2006)
- Risk of grades 2-4 aGVHD: Multiple regression analysis

Risk Factor	RR of aGVHD (95% CI)	P-value
Single UCBT Double UCBT	1 2	0.01
Myeloablative Nonmyeloablative	1 1.7	0.01
No ATG ATG	1 0.5	0.02

- Use of ATG had no significant impact on overall treatment related mortality

Blood. 2009;113:2410-15

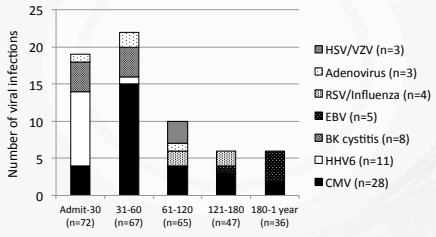
Double UCBT without ATG: MSKCC Study

- Enrolled 72 patients receiving double UCBT for hematologic malignancies (2005-2009)
  - Myeloablative (n = 34)
  - Reduced intensity myeloablative (n = 18)
  - Nonmyeloablative (n = 20)
  - GVHD Prophylaxis: Calcineurin inhibitor + MMF
- Sustained donor engraftment: 94%
- Cumulative incidence of grade 2-4 aGVHD was 43%
  - Grade 2: 12 (39%)
  - Grade 3: 15 (48%)
  - Grade 4: 4 (13%)

Biol Blood Marrow Transplant. 2011;17:1460-67

Double UCBT without ATG: MSKCC Study

- 75% of patients were free of serious infections at day +120
- All infections occurring after day +120 were associated with GVHD/corticosteroid use



Biol Blood Marrow Transplant. 2011;17:1460-67

UCBT: Early, Late, or no ATG

- Retrospective analysis at 2 pediatric HCT centers
- Myeloablative and RIC regimens for single UCBT
- Treatment Groups (rATG Thymoglobulin):
  - Late rATG + CSA/pred (10mg/kg, divided, d -5 to -1, n = 48)
  - Early rATG + CSA/pred (10mg/kg, divided, d -9 to day -5, n = 33)
  - No ATG + CSA/MMF (n= 46)
- Immune reconstitution (CD3+, CD4+ and CD4+naive cells) measured at 1, 2, 3, 6, and 12 months post-UCBT

Blood. 2014; 123:126-32.

UCBT: Early, Late, or no ATG

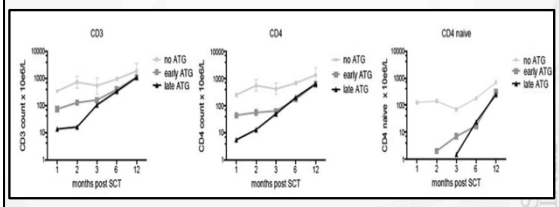
Outcome	No ATG	Early rATG	Late rATG	P-value (No ATG vs. Early rATG)	P-value (Early vs. Late rATG)
aGrade 2-4	60%	44%	14%	**<0.01**	**<0.01**
aGrade 3-4	31%	18%	5%	**0.02**	0.15
cGVHD	12%	11%	28%	NS	NS

- Increased aGVHD in the no ATG and early ATG groups
- No difference in engraftment, NRM, EFS, relapse, OS

Blood. 2014; 123:126-32.

UCBT: Early, Late, or no ATG

- Increased CD3+, CD4+ and CD4+ naïve Tcells in the no ATG group at all time points vs. ATG groups (p = <0.01)
- Increased CD3+, CD4+ and CD4+ naïve Tcells in the early ATG group at 1 (p = 0.02) and 2 (p = 0.04) months vs. late ATG group

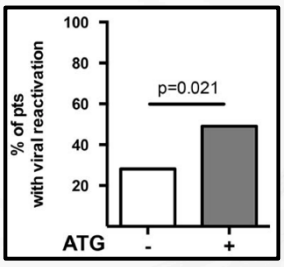


Blood. 2014; 123:126-32.

UCBT: Early, Late, or no ATG

Viral reactivation in the no ATG group vs. ATG groups

- Decreased overall viral reactivation in patients not receiving ATG (p 0.02)
- Decreased death due to viral reactivation in patients not receiving ATG (p <0.01)



Blood. 2014; 123:126-32.

UCBT RIC: EBMT Study

- Retrospective registry analysis of adult patients with hematologic malignancies who received single or double UCBT (2004 - 2011)
- RIC with TBI-fludarabine-cyclophosphamide
- CSA + MMF GVHD prophylaxis in 91% of patients
- Treatment Groups
  - rATG (Thymoglobulin) at a median dose of 8mg/kg or ATG-F (ATG-Fresenius) at a median dose of 20mg/kg (n = 82)
  - No ATG (n = 579)

Blood. 2013; 122(21): Abstract 412

UCBT RIC: EBMT Study

- Multivariate analysis
- Type and dose of ATG not associated with outcomes

	No ATG	rATG/ATG-F	HR (95% CI)	P-value
aGVHD	41%	15%	0.31 (0.17-0.55)	**<0.01**
cGVHD @ 3y	29%	20%	NS	0.07*
Relapse @ 3y	34%	29%	NS	0.6*
NRM @ 3y	26%	46%	1.68 (1.16-2.43)	**<0.01**
OS @ 3y	48%	30%	1.69 (1.19-2.4)	**<0.01**

*P-values from univariate analysis
rATG: Rabbit ATG Thymoglobulin, ATG-F: ATG Fresenius, NRM: non-relapse mortality, OS: overall survival

- 72% of deaths in ATG group due to infection vs 39% in the no ATG group ($p < 0.01$)

Blood. 2013; 122(21): Abstract 412

ATG in Umbilical Cord Blood Transplant: Conclusions

- Removal of ATG results in higher aGVHD which may partially negate beneficial effects of a reduction in infections
  - Patients should be closely monitored for late infections
- Increase in infection with ATG impacts NRM more significantly than an increase in GVHD without ATG, resulting in inferior OS with the use of ATG following TBI-Flu-Cy conditioning
- RCTs of ATG use in UCBT are needed

Audience Response Question #2

Retrospective registry data suggests an increased risk of relapse and inferior overall survival when ATG is used in this setting:

A. Myeloablative conditioning with an unrelated donor
B. Myeloablative conditioning with a related donor
C. Reduced intensity conditioning
D. Umbilical cord blood transplant

Audience Response Question #3

Retrospective registry data suggests an increased risk of infection and inferior overall survival when ATG is used in this setting:

A. Myeloablative conditioning with an unrelated donor
B. Myeloablative conditioning with a related donor
C. Reduced intensity conditioning
D. Umbilical cord blood transplant

How should ATG hypersensitivity be managed in immunosuppressive therapy for aplastic anemia?

Patient Case

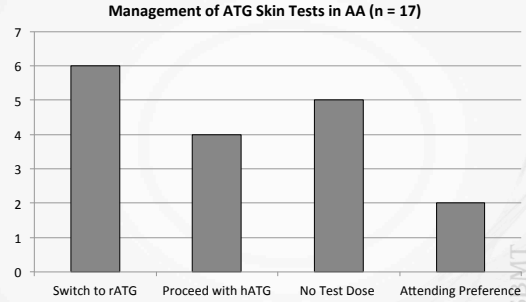
AP is a 21 yom with severe aplastic anemia (SAA). He does not have a sibling match for HCT and is admitted for immunosuppressive therapy (IST) with horse ATG and cyclosporine (CSA). He received horse ATG 5mcg (0.1mL of a 1:1000 dilution) intradermal as a test dose and immediately developed a 15mm wheal and flare hypersensitivity reaction with wheezing and complaints of shortness of breath.

Audience Poll

How would you handle the results of AP's horse ATG skin test?

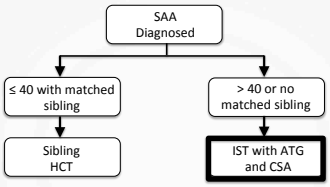
A. Switch to rabbit ATG
B. Proceed with horse ATG
C. Not applicable – We do not perform ATG skin tests at my institution
D. Attending preference
E. I don't know

ASBMT Listserve Question Results



ASBMT Pharmacy Google Listserve Commmunication. June 2013.

Treatment Algorithm for SAA



- Horse ATG widely used for IST in AA since the 1980s
- Rabbit ATG used in salvaging patients with relapsed/ refractory AA after initial hATG
- Horse ATG (Lymphoglobuline) withdrawn in 2007
  - Stimulated study of rATG as first line therapy

Blood. 2012;120:1185-96

Horse vs. Rabbit ATG in AA: NIH Study

- Randomized, prospective trial of 120 patients with SAA conducted between 2005 – 2010 at the NIH
  - hATG 40mg/kg/day IV x 4 days + CSA
  - rATG 3.5mg/kg/day IV x 5 days + CSA

Outcome	hATG (n = 60)	rATG (n = 60)	P value
HR at 3 months	37 (62%)	20 (33%)	0.002
HR at 6 months	41 (68%)	22 (37%)	<0.001
OS at 3 years	96%	76%	0.04

hATG: Horse ATG (ATGAM), HR: hematologic response, OS: overall survival

N Engl J Med. 2011;365:430-8

Horse vs. Rabbit ATG in AA: Conclusions

- Horse ATG + CSA is associated with superior HR and OS versus rabbit ATG + CSA for first-line IST in SAA
- British Committee for Standards in Haematology AA Writing Committee/European Group for Blood and Marrow Transplantation SAA Working Party
  - Urgent addendum to the 2009 AA guidelines
  - Horse ATG (ATGAM) is recommended as first line IST

N Engl J Med. 2011;365:430-8 / Letter from the BCSH AAWC. 2011. Available at: bcshguidelines.com

Horse ATG (ATGAM®)

- PI recommends intradermal injection of 0.1mL of a 1:1,000 dilution observed for 1 hour prior to infusion
  - ≥ 10mm local reaction with a wheal and/or erythema is considered a positive test
  - False negatives and positives may occur
- Positive skin test result
  - Weigh risk and benefit, consider alternative therapies
- Systemic reactions (rash, tachycardia, hypotension, dyspnea) or anaphylaxis precludes administration

Should we follow these recommendations?

Atgam PI. Kalamazoo, MI: Pharmacia; 2005

Horse ATG Desensitization

Case	Desensitization Protocol	Outcome
Bielory (1988) 6yof, AA 8mm wheal	**Supportive Care**: ICU transfer, pre-medication started 24h prior to desensitization **Desensitization**: Increasing concentrations and rates of ID, subq, and IV administration q 10min **Treatment**: 15mg/kg IV over 24h daily x 10 doses	Completed full dose
Hall (2006) 4yom, SAA 14mm wheal	**Supportive Care**: ICU transfer, premedications **Desensitization**: Increasing concentrations and rates, IV administration q 10min **Treatment**: 40mg/kg IV over 10h daily x 4 doses	Completed full dose w/ rate reductions, PRN H_1R antagonist
Ferdman (2004) 17yom, AA 20mm wheal, hypotension	**Supportive Care**: ICU transfer, premedications **Desensitization**: Continuous infusion approach **Treatment**: 40mg/kg IV over 24h daily x 4 doses	Completed full dose, PRN H_1R antagonist

JAMA. 1988;260:3164-67 / *Am J Health Syst Pharm*. 2006;63:1633-6 / *Transplantation*. 2004;77:321-23

Managing ATG Hypersensitivity in IST for Aplastic Anemia: Conclusions

- Changing ATG formulations from horse to rabbit should not be used as a strategy to manage positive skin tests
- Consider holding B-blockers before ATG to avoid suppressing physiologic compensatory responses to anaphylaxis
- Skin testing may identify patients who would benefit from hATG desensitization, more aggressive pre-medications and a higher acuity of care
- Hypersensitivity reactions may develop in patients with negative skin tests

Ann Allergy Asthma Immunol. 2000;85:311-16 / Atgam PI. Kalamazoo, MI: Pharmacia; 2005 / *Blood*. 2012;120:1185-96

What have we learned after 30 years of controversy?

- The use of ATG in HCT preparative regimens should be individualized based on stem cell source, preparative regimen intensity, primary disease, and ATG preparation, dose and schedule
- Large, randomized controlled trials are needed
- Horse ATG is the preferred ATG preparation for immunosuppressive therapy in aplastic anemia
- Changing ATG formulations from horse to rabbit should not be used as a strategy to manage positive skin tests

Antithymocyte Globulin (ATG) Dosing and Controversies

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