Infectious Complications Associated with the Use of Antithymocyte Globulin in Reduced Intensity Allogeneic Transplants

Kara E. Loth, PharmD
Hematology/Oncology Specialty Resident

Wake Forest Baptist Health
Disclosure

Disclosure statement: these individuals have the following to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation.

Resident: Kara Loth (nothing to disclose)

Project Director & Co-Investigators: Seema Naik, LeAnne Kennedy, Greg Russell, Denise Levitan, Kenneth Zamkoff, David Hurd (nothing to disclose)
Wake Forest Baptist Health

- Winston-Salem, NC
- Academic teaching facility
- NCI-designated Comprehensive Cancer Center
- Approximately 100 bone marrow transplants are conducted annually
Antithymocyte Globulin (ATG)

- Polyclonal immunoglobulin utilized in reduced intensity conditioning allogeneic stem cell transplant (RIC allo-SCT)
- Produced by immunizing rabbits (Thymoglobulin®) and horses (Atgam®) with human thymocytes
- The antibodies produced destroy human leucocytes in the transplant recipient
  - Reduce the T-cells that could produce graft rejection
  - Inhibit donor cells that could induce graft versus host disease (GVHD)

Risk of Infection

- Variability in the amount of myelosuppression with RIC therapy
  - Degree of myelosuppression is less
  - Extent of lymphodepletion is greater

- Lymphocyte recovery is a prolonged process

- Aplastic period (neutropenia)
- Neutrophil recovery period (major T-cell dysfunction)
- Recovery of B-cells and CD4+ T-cells

Purpose

Analyze the type and incidence of infectious complications in RIC allo-SCT patients treated with or without rabbit antithymocyte globulin.
Primary Outcome

- Rate of infection from engraftment to one year after RIC allo-SCT
  - Bacterial infection
  - Fungal infection
  - Viral infection
    - Cytomegalovirus (CMV)
    - Herpes simplex virus (HSV)
    - Epstein Barr virus (EBV)
    - BK virus
Secondary Outcomes

- Rate of infection during the engraftment period of RIC allo-SCT
- Incidence of acute and chronic GVHD
- Overall survival at 1 year
- Disease-free status at 1 year
**Methods**

- Retrospective, cohort study
- Patients identified from a computer-generated list
- IRB-approved

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≥18 years with hematologic malignancy</td>
<td>• Aplastic Anemia</td>
</tr>
<tr>
<td>• RIC allogeneic stem cell transplant between January 2001 and December 2010</td>
<td>• Deceased within 30 days of treatment</td>
</tr>
</tbody>
</table>
Data Collection

- Patient demographics
- Conditioning regimen
- Date of engraftment
- Incidence of infection
  - Bacterial
  - Fungal
  - Viral
- Graft versus host disease
- Survival and disease-free status at 1 year
Statistical Analysis

- Student’s t-test for continuous data
- Fisher’s exact test for nominal data
Patient Population

65 Patients Identified

2 Patients Excluded

31 Patients Treated with ATG

32 Patients Treated without ATG
## Patient Demographics

<table>
<thead>
<tr>
<th>Patients</th>
<th>ATG (n=31)</th>
<th>No ATG (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, years (+/- SD)</td>
<td>58.9 +/- 10.0</td>
<td>61.6 +/- 5.5</td>
<td>NS</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>21 (67.7)</td>
<td>21 (65.6)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Disease Type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML, n (%)</td>
<td>22 (71)</td>
<td>17 (53.1)</td>
<td>NS</td>
</tr>
<tr>
<td>MDS, n (%)</td>
<td>4 (12.9)</td>
<td>9 (28.1)</td>
<td>NS</td>
</tr>
<tr>
<td>CML, n (%)</td>
<td>0</td>
<td>2 (6.2)</td>
<td>NS</td>
</tr>
<tr>
<td>NHL, n (%)</td>
<td>2 (6.5)</td>
<td>1 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple Myeloma, n (%)</td>
<td>1 (3.2)</td>
<td>1 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>APL, n (%)</td>
<td>1 (3.2)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>ALL, n (%)</td>
<td>1 (3.2)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>CLL, n (%)</td>
<td>0</td>
<td>1 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Myelofibrosis, n (%)</td>
<td>0</td>
<td>1 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Donor Type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRD, n (%)</td>
<td>0</td>
<td>32 (100)</td>
<td></td>
</tr>
<tr>
<td>MUD, n (%)</td>
<td>29 (93.5)</td>
<td>0</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>mMRD, n (%)</td>
<td>2 (6.7)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Primary Results: Patients with Infection

No ATG

- Infection: 44%
- No Infection: 56%
- n=32

ATG

- Infection: 19%
- No Infection: 81%
- n=31

p=NS
Patients with a Single Infection

![Bar chart showing the number of patients with bacterial, fungal, and viral infections with and without ATG treatment.](chart.png)

- **Bacterial Infections**
  - ATG: 7 patients
  - No ATG: 8 patients
- **Fungal Infections**
  - ATG: 0 patients
  - No ATG: 0 patients
- **Viral Infections**
  - ATG: 5 patients
  - No ATG: 0 patients

The difference in bacterial infections between patients with and without ATG treatment is statistically significant with a p-value of 0.024.
Patients with Multiple Infections

No ATG
n=32

- Viral + bacterial: 9.4%
- Fungal + bacterial: 6.3%
- Viral + fungal: 3.1%

ATG
n=31

- Viral + bacterial: 32.3%
- Fungal + bacterial: 6.5%
- Viral + fungal + bacterial: 6.5%

$p=0.032$
## Infection During Engraftment Period

<table>
<thead>
<tr>
<th>Patients with Infection</th>
<th>ATG (n=31)</th>
<th>No ATG (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Infection Only, n (%)</td>
<td>5 (16.1)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Fungal Infection Only, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Viral Infection Only, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Multiple Infections, n (%)</td>
<td>1 (3.2)</td>
<td>3 (9.4)</td>
</tr>
</tbody>
</table>

$p=NS$
# Graft vs. Host Disease

## Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>ATG (n=31)</th>
<th>No ATG (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GVHD, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Chronic GVHD, n (%)</strong></td>
<td>5 (16.1%)</td>
<td>6 (18.8%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*p*=NS
Outcomes

Disease-Free Status

Percent Without Relapse

Months

No ATG  ATG

Survival

Percent Living

Months

No ATG  ATG

p=NS
Limitations

- Small sample size
- Retrospective evaluation
- Reliance on accurate chart documentation
- Baseline demographics differed between study groups
Conclusions

- There was an increased rate of infections in patients treated with ATG.

- In particular, the incidence of multiple infections as well as viral infections alone was significantly increased in the ATG group.

- The incidence of GVHD was not significantly different between the study groups.
Future Directions

- Present data to BMT Faculty
- Consider reducing immunosuppression in MUD RIC allo SCT
- Follow up evaluation
Self-Assessment Question

True/False

There is an increased incidence of infection in patients treated with antithymocyte globulin in RIC allogeneic stem cell transplants?

True - There is an association between the use of ATG and an increased incidence of infection however, a cause and effect relationship has not been established.
Acknowledgements

- Seema Naik, MD
- LeAnne Kennedy, PharmD, BCOP
- Gregory Russell, MS
- Denise Levitan, MD
- Kenneth Zamkof, MD
- David Hurd, MD
Infectious Complications Associated with the Use of Antithymocyte Globulin in Reduced Intensity Allogeneic Transplants

Kara E. Loth, PharmD
Hematology/Oncology Specialty Resident
Wake Forest Baptist Health
Winston-Salem, NC