Therapy of Severe Aplastic Anemia With Anti-Human Thymocyte Globulin and Androgens: The Effect of HLA-Haploidentical Marrow Infusion

By Kristine Doney, Steven J. Dahlberg, Deborah Monroe, Rainer Storb, C. Dean Buckner, and E. Donnall Thomas

Fifty-four patients with severe aplastic anemia were treated with horse anti-human thymocyte globulin (ATG) and androgens. Thirty of these patients also received an infusion of HLA-haploidentical marrow cells. Only those patients having evidence of hematologic recovery within 3 mo after ATG therapy were considered responders to the immunosuppressive regimen. Of 53 patients evaluable for response, 21 had complete or partial responses and 7 had minimal improvement by defined criteria. The remaining patients did not respond or died. Factors correlated with response to therapy included a short duration of aplasia and high admission granulocyte count. Thirty-six patients did not respond or died. Factors correlated with survival, as did younger age. Four patients with complete or partial responses had a recurrence of severe aplasia 6–17 mo after their first course of ATG. Three of these patients were retreated with ATG (and oxymethalone in two cases). All three had second responses to therapy, but two of the three had second relapses. The fourth patient responded to oxymethalone alone, but died after a second relapse. Mismatched marrow infusion had no effect on the incidence of response or survival.

IMMUNOSUPPRESSIVE therapy for severe aplastic anemia has been reported to result in hematologic improvement in 30%–60% of treated patients.1 The efficacy of anti-human lymphocyte globulin (ALG) or antithymocyte globulin (ATG) preparations, compared to supportive care alone, has been demonstrated in two recent prospective randomized studies.6,7 ATG has been used alone as single-modality therapy or in combination with HLA-haploidentical marrow infusion and/or androgenic steroids. Initial reports suggested that mismatched-marrow infusion enhanced the degree of hematologic recovery.8 However, there has been no demonstrated benefit in survival for those patients who received a marrow infusion following ALG.1

The current study was designed to treat a series of patients with severe aplastic anemia with a course of ATG and androgens. For those patients with donors who were identical for one HLA haplotype, marrow cells were also infused. This report summarizes the results of immunosuppressive therapy for severe aplastic anemia in 54 patients and evaluates the role of HLA-haploidentical marrow infusion and pretreatment factors on hematologic recovery and survival.

MATERIALS AND METHODS

Fifty-six patients were treated between November 1979 and January 1982. Consent was obtained from all patients and their respective marrow donors. The protocol and consent forms were approved by the Human Subjects Review Committee of the Fred Hutchinson Cancer Research Center. Two patients did not fulfill the criteria for severe aplastic anemia, as defined by the International Aplastic Anemia Study Group,9 and were therefore excluded from the subsequent analysis. Admission data from the remaining 54 patients are summarized in Table 1.

All patients received standard supportive care, including red blood cell and platelet transfusions and institution of broad-spectrum intravenous antibiotics when fever developed and granulocyte counts were ≤500/cu mm. In general, the hematocrit was maintained between 25% and 30% and the platelet count at ≥20,000/cu mm. Only one patient received therapeutic granulocyte transfusions. Isolation procedures utilized private rooms, hand washing, and the use of face masks.

Prior to therapy, all patients had negative intradermal tests to a 1:1,000 dilution of normal horse serum and a 1:1,000 dilution of horse ATG (ATGAM, Upjohn Company, Kalamazoo, MI, lot 17908). Patients then received ATG, 16 mg/kg/day intravenously for 10 days. Each daily dose was diluted in 1–2 liter of half-normal or normal saline and infused over 6–12 hr. Most patients had Hickman right atrial catheters inserted for intravenous access.10 Premedications for the ATG infusions included diphenhydramine, acetaminophen, and/or meperidine. Severe reactions (high fever, pruritic skin eruptions, arthralgias) were treated with hydrocortisone, prednisone, or methylprednisolone equivalent to prednisone. 1 mg/kg/day, in 51 patients.

Twenty-four to 48 hr after completing ATG therapy, 30 patients received marrow infusion from family members with whom they were identical for one HLA haplotype. Donors and recipients were required to be ABO-compatible and lymphocytoxic crossmatch-negative. The marrow aspiration technique has been described.11 Between 0.5 and 5.3 × 108 (median 2.1 × 108) nucleated cells/kg recipient body weight were infused. Twenty-four patients did not receive marrow cells. These latter patients either had no family members who met the above criteria, who were in good health, or who were willing or able to come to Seattle. There was no difference between patients who did and who did not receive marrow with...
that in our previous study, although the duration of
TREATMENT OF APLASTIC ANEMIA WITH ATG
was

ATG therapy differed (1 0 days
versus 4 days, respec-
tively). In this study 41 patients (76%) developed a symptom (complex fever, rash, and/or arthralgias) compatible with serum sickness. Four patients received less than the 10 prescribed doses (4, 8, 9, and 9.6 doses). Reasons for discontinuation were (1) development of pneumonia (two patients), (2) refractoriness to platelet transfusions (one patient), and (3) increased systemic reaction during the last ATG infusion (one patient).

Hematologic Recovery

Fifty-three patients were evaluable for response to therapy. One additional patient was not evaluable after undergoing fetal liver transplantation at another institution less than 3 mo after receiving ATG. According to the previously listed criteria, 11 patients had a complete response, 10 had a partial response, 7 showed minimal improvement, and 25 were nonre-
sponders. A summary of the blood counts of the 21 patients classified as complete or partial responders is shown in Table 2. Median time to maximum response was 2.7 mo (range 0.8–8.3) for complete responders and 3.6 mo (range 2.2–6.2) for partial responders.

Of the 21 patients who eventually achieved either a complete or partial response, 4 have had a recurrence of severe asplasia. Table 3 summarizes their courses of therapy. For the two patients (unique patient number [UPN] 1290 and 1234) retreated in Seattle, methyl-
prednisolone, 60–100 mg, was used as premedication for ATG in addition to diphenhydramine and acetaminophen. Toxicity was similar to that occurring in patients receiving a first course of therapy. All four patients achieved a second complete or partial response, but three had a second relapse 10–14 mo after their first relapse. Two of the three (UPNs 1290 and 1345) remain aplastic, and one (UPN 1184) has died of hemorrhage 34 mo after receiving ATG. The fourth patient (UPN 1199) had a second sustained complete response and is now surviving 30 mo after the second course of ATG.

Of the 32 patients who had minimal improvement or no response to ATG therapy, 8 have subsequently became transfusion-independent. Of 7 patients with minimal improvement, 3 slowly became transfusion-independent with platelet counts ranging between 60 × 10^3 and 108 × 10^3/cu mm. Granulocyte counts increased to >1,000/cu mm 7–14 mo after treatment. Three still require transfusions, and one has died. Of 25 nonresponders, 4 have recovered with supportive care plus androgen and/or corticosteroid therapy 7–17 mo after receiving ATG. These four patients are all transfusion-independent, with platelet counts between 53 × 10^3 and 200 × 10^3/cu mm and have >1,000

respect to age, sex, etiology of aplasia, duration of aplasia, or admission granulocyte count.

On day 12 (day 1 was defined as the first day of ATG therapy), oxymethalone, 3 mg/kg p.o. daily for 3 mo, was initiated. Patients with no evidence of hematologic improvement at 3 mo were consid-
ered nonresponders and had their oxymethalone discontinued. Patients exhibiting hematologic improvement at 3 mo had oxymeth-
alone therapy tapered over 4–8 wk, usually after attaining a plateau of their counts.

Patients were hospitalized in Seattle until completion of their ATG therapy and marrow infusion or until resolution of any acute infection. Duration of hospitalization ranged from 11 to 61 (median 20) days. After discharge, patients were cared for by their referring physicians.

Only patients who had evidence of hematologic improvement within 3 mo after therapy were considered to have "responded" to ATG therapy. The degree of response was defined by the subsequent sustained level of improvement as follows: (1) complete response—return of a normal hematocrit, granulocyte count ≥1,000/cu mm, and a platelet count of ≥100,000/cu mm; (2) partial response—improvement in all three cell lines, granulocyte count ≥500/cu mm, absence of infections, and no transfusion requirement; (3) minimal improvement—increase in granulocyte count by ≥500/cu mm but transfusions still required; and (4) no improvement—patient remained severely aplastic at 3 mo or died.

The Cox regression method was used to simultaneously relate the levels of potential prognostic factors to patient survival. A binary logistic regression model was used to relate prognostic factors to hematologic recovery. The Kaplan-Meier product limit method was used to obtain the survival curves.

RESULTS

Toxicity

Toxicity associated with ATG administration and marrow infusion in this study was not different from that in our previous study, although the duration of ATG therapy differed (10 days versus 4 days, respec-

Time from diagnosis of severe aplasia to initial ATG therapy.
†Drugs implicated: gold (five patients), quinacrine (one patient).
§Other etiologies: hepatitis, pregnancy, and paroxysmal nocturnal hemoglobinuria.
\[Other prior therapy: lithium (five patients); vincristine (three patients); etiocholanolone (one patient).

<table>
<thead>
<tr>
<th>Table 1. Admission Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Sex (male-female)</td>
</tr>
<tr>
<td>Disease duration (mo)*</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Etiology of aplasia (number of patients)</td>
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<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Drug†</td>
</tr>
<tr>
<td>Other§</td>
</tr>
<tr>
<td>Prior therapy (number of patients)</td>
</tr>
<tr>
<td>Androgens</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
</tbody>
</table>

*Time from diagnosis of severe aplasia to initial ATG therapy.
†Drugs implicated: gold (five patients), quinacrine (one patient).
§Other etiologies: hepatitis, pregnancy, and paroxysmal nocturnal hemoglobinuria.
\[Other prior therapy: lithium (five patients); vincristine (three patients); etiocholanolone (one patient).
Table 2. Peripheral Blood Counts of 21 Patients With Complete or Partial Responses

<table>
<thead>
<tr>
<th></th>
<th>Hematocrit (%)</th>
<th>White Blood Count/cu mm (x 10^3)</th>
<th>Neutrophils/cu mm (x 10^3)</th>
<th>Platelets/cu mm (x 10^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete responders (11 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Values at 3 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>21-44</td>
<td>1.8-8.1</td>
<td>0.6-5.9</td>
<td>30-400</td>
</tr>
<tr>
<td>Median</td>
<td>38.0</td>
<td>3.5</td>
<td>1.8</td>
<td>118</td>
</tr>
<tr>
<td>Mean</td>
<td>35.8</td>
<td>3.9</td>
<td>2.2</td>
<td>163</td>
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<tr>
<td>Values at time of maximum recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>36-51</td>
<td>2.6-10.2</td>
<td>1.1-7.3</td>
<td>102-400</td>
</tr>
<tr>
<td>Median</td>
<td>38.5</td>
<td>5.7</td>
<td>2.4</td>
<td>198</td>
</tr>
<tr>
<td>Mean</td>
<td>39.8</td>
<td>5.3</td>
<td>3.0</td>
<td>195</td>
</tr>
<tr>
<td>Partial responders (10 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Values at 3 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>27-46*</td>
<td>1.9-5.2</td>
<td>0.6-3.1†</td>
<td>22-120‡</td>
</tr>
<tr>
<td>Median</td>
<td>36.8</td>
<td>2.9</td>
<td>1.4</td>
<td>41</td>
</tr>
<tr>
<td>Mean</td>
<td>36.8</td>
<td>3.2</td>
<td>1.7</td>
<td>51</td>
</tr>
<tr>
<td>Values at time of maximum recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>28-46</td>
<td>2.0-5.2</td>
<td>0.7-3.1</td>
<td>28-98</td>
</tr>
<tr>
<td>Median</td>
<td>35.5</td>
<td>2.8</td>
<td>1.4</td>
<td>46</td>
</tr>
<tr>
<td>Mean</td>
<td>36.7</td>
<td>3.3</td>
<td>1.8</td>
<td>52</td>
</tr>
</tbody>
</table>

*Excludes two patients who were still receiving red blood cell transfusions.
†Data based on 9 patients. One patient did not have a differential count done at 3 mo.
‡Excludes two patients who were still receiving platelet transfusions.

granulocytes/cu mm. One nonresponder recovered after receiving high-dose 6-methylprednisolone therapy.\(^{13}\) Three of the 25 patients remain severely aplastic (one after failing high-dose steroid therapy) 15.5-26 mo after receiving ATG. One patient was lost to follow-up on day 581 with stable disease and 16 have died. Thus, of the 53 patients who are evaluable for response, 27 are transfusion-independent and 6 still require red blood cell and/or platelet transfusions. Two patients have been lost to follow-up (1 with recurrent aplasia) and 18 have died (1 after a second relapse).

Multivariate logistic regression analysis comparing complete plus partial responders to minimal and nonresponders revealed two covariates significantly correlated with response: (1) a shorter duration of time from diagnosis to ATG therapy \((p = 0.0002)\) and (2) a higher absolute granulocyte count prior to receiving ATG \((p = 0.003)\) (Table 4).

The addition of marrow infusion to ATG and androgens was not associated with an increased incidence of hematologic recovery \((p = 0.47)\). Among the patients who did or did not receive marrow, there was no difference between the two groups with respect to duration of aplasia or admission granulocyte count.

Etiology of the aplasia was not considered in the regression analysis because of the small number of patients (nine) with “known” causes. Of the five patients with gold-induced aplasia, two had complete responses and one had a partial response. The patient with presumed quinacrine-related disease had a partial response, and the patient with hepatitis-associated aplasia had only minimal improvement in granulocyte count followed by slow partial recovery of all cell lines. The remaining four patients were nonresponders.

Survival

As of July 1, 1983, 36 patients are alive and 18 have died. Three of the 54 patients were censored at days 64, 581, and 649, respectively, when they were lost to follow-up. Only two of the patients who died had evidence of hematologic recovery prior to death. Both of these patients died of hemorrhage, one after improvement in granulocyte counts only and one after a second relapse. The range of follow-up for surviving patients is 18-43 (median 26) mo. Causes of death were infection (10 patients), hemorrhage (5 patients), infection plus hemorrhage (2 patients), and adult respiratory distress syndrome (1 patient).

Cox multivariate regression analysis of the effect of clinical parameters on survival also showed a positive correlation with a high admission absolute granulocyte count \((p = 0.003)\) and a short duration of time from diagnosis to ATG therapy \((p = 0.046)\) (Table 5). In addition, an increased mortality was associated with patients over 40 yr of age \((p = 0.038)\). There was no association of marrow infusion with improved survival \((p = 0.26)\). Kaplan-Meier survival estimates, comparing patients who did and did not receive a marrow infusion, are shown in Fig. 1.

**DISCUSSION**

The role of immunosuppressive therapy in aplastic anemia has been examined by numerous investigators.
Components of the regimens studied have included an immunosuppressive agent with or without subsequent infusion of HLA-haploidentical marrow cells and with or without supplemental androgenic steroid therapy. Immunosuppressive agents have included cyclophosphamide, ALG, ATG, and 6-methylprednisolone.181319 Although in vitro data suggest that hematologic recovery may be the result of eliminating a population of T lymphocytes that have suppressed normal stem cell differentiation, conclusive in vivo data for this mechanism are lacking.20–24 Assessing the value of immunosuppressive therapy in aplastic anemia has been complicated by the multiagent regimens employed, the heterogeneity of the immunosuppressive agents, and the disease itself, which is associated with a low but definite probability of spontaneous recovery.

The use of marrow infusion following ALG therapy was first reported by Mathe et al.2526 The intent of these initial studies was to attain permanent engraftment of HLA-mismatched donor cells in patients with either aplasia or hematologic malignancies. Using various markers, including karyotypes, red cell antigens, immunoglobulin allotypes, or donor skin graft tolerance, only transient hematopoietic chimerism was demonstrated in the patients studied. No patient developed graft-versus-host disease. Three of seven patients with aplastic anemia partially recovered autologous marrow function.

Speck et al. subsequently used a rabbit model of benzene- or 32P-induced aplasia to evaluate the efficacy of antilymphocyte serum and marrow infusion.2728 In both studies, marrow infusion alone had no effect. Antilymphocyte serum plus marrow infusion resulted in transient engraftment and split immunologic chimerism. Continued follow-up of surviving 32P-treated animals revealed autologous marrow recovery. On the basis of these data, it was postulated that antilymphocyte serum and marrow infusion, by pro-

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**Table 3. Clinical Course of Four Patients With Recurrent Aplastic Anemia**

<table>
<thead>
<tr>
<th>Unique Patient Number</th>
<th>Initial Therapy*</th>
<th>Initial Response†</th>
<th>Time to Relapse (mo)‡</th>
<th>Secondary Therapy§</th>
<th>Response to Secondary Therapy</th>
<th>Second Relapse</th>
<th>Time From 1st to 2nd Relapse (mo)</th>
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<tbody>
<tr>
<td>1184</td>
<td>ATG, BM, OXY</td>
<td>PR</td>
<td>17.0</td>
<td>OXY</td>
<td>CR</td>
<td>Yes</td>
<td>14</td>
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<tr>
<td>1199</td>
<td>ATG, BM, OXY</td>
<td>CR</td>
<td>6.5</td>
<td>ATG, OXY</td>
<td>CR</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>1290</td>
<td>ATG, BM, OXY</td>
<td>CR</td>
<td>14.5</td>
<td>ATG</td>
<td>PR</td>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>1345</td>
<td>ATG, OXY</td>
<td>PR</td>
<td>6.0</td>
<td>ATG, OXY</td>
<td>PR</td>
<td>Yes</td>
<td>12</td>
</tr>
</tbody>
</table>

*ATG, horse anti-human thymocyte globulin; doses as described in text. BM, haploidentical bone marrow infusion. OXY, oxymetholone.
†CR, complete response; PR, partial response, as defined in text.
‡Calculated from date of first dose of ATG to date of recurrence of severe aplasia.
§ATG and oxymetholone dosages for patients 1290 and 1345 are as defined in text. Patient 1199 received University of Minnesota horse ATG and oxymetholone, doses unknown.

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**Table 4. Factors Related to Response: Multivariate Logistic Regression Comparing Complete or Partial to Minimal or No Response**

<table>
<thead>
<tr>
<th>Factor†</th>
<th>Number of Patients</th>
<th>Complete or Partial Response</th>
<th>Minimal Improvement or No Response</th>
<th>Two-sided p Value‡</th>
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</thead>
<tbody>
<tr>
<td>Time from diagnosis to ATG therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 mo</td>
<td>18</td>
<td>15</td>
<td>0.0002</td>
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</tr>
<tr>
<td>&gt;2 mo</td>
<td>3</td>
<td>17</td>
<td></td>
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<tr>
<td>Granulocyte count</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>0–99/cu mm</td>
<td>6</td>
<td>20</td>
<td></td>
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<tr>
<td>100–499/cu mm</td>
<td>7</td>
<td>7</td>
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<tr>
<td>≥500/cu mm</td>
<td>8</td>
<td>5</td>
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<tr>
<td>Marrow infusion</td>
<td>Yes</td>
<td>12</td>
<td>17</td>
<td>0.47</td>
</tr>
<tr>
<td>No</td>
<td>9</td>
<td>15</td>
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*Analysis was based on 53 patients, as one patient was not evaluable for response.
†Other factors evaluated that were not significantly associated with response included active infection at admission, infections occurring during ATG therapy, serum sickness, previous therapy for aplastic anemia, red blood cell transfusion requirement, platelet transfusion requirement, admission white blood count, admission hematocrit, admission platelet count, patient sex, donor sex (patients not receiving marrow infusion were excluded).
‡From Chi-square statistic based on log likelihood.

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**Table 5. Factors Related to Survival: Multivariate Cox Regression**

<table>
<thead>
<tr>
<th>Factor†</th>
<th>Relative Risk of Death</th>
<th>Two-sided p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from diagnosis to ATG therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 mo</td>
<td>1.0</td>
<td>0.046</td>
</tr>
<tr>
<td>&gt;2 mo</td>
<td>2.8</td>
<td></td>
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<tr>
<td>Granulocyte count</td>
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<td></td>
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<tr>
<td>0–99/cu mm</td>
<td>1.0</td>
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<td>100–499/cu mm</td>
<td>0.3</td>
<td>0.003</td>
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<tr>
<td>≥500/cu mm</td>
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<td>Age (yr)</td>
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<td>20–40</td>
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<td>&gt;40</td>
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*Other factors evaluated that were not significantly associated with survival were as follows: active infection at admission, infection occurring during ATG therapy, serum sickness, previous therapy for aplastic anemia, red blood cell transfusion requirement, platelet transfusion requirement, admission white blood count, admission hematocrit, admission platelet count, patient sex, and donor sex (patients not requiring marrow infusion excluded).
show any clinically significant difference between
quent analysis of larger numbers of patients failed to
complete" in patients given ALG and marrow. Subse-
out mismatched marrow infusion and androgen ther-
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HLA-haploidentical marrow infusion. Data are as of 7/1/83. (\(\beta\)) ATG and androgen therapy with
all patients had suitable donors by the defined criteria.
patients with severe aplasia. Patients were not random-
treatment groups.'

Subsequent human studies of ALG with and without mismatched marrow infusion and androgen therapy initially indicated that the addition of mismatched marrow infusion to ALG and androgen therapy resulted in similar numbers of patients recovering marrow function. However, remissions were "more complete" in patients given ALG and marrow. Subsequent analysis of larger numbers of patients failed to show any clinically significant difference between treatment groups.1

In the current study, we evaluated the role of marrow infusion with ATG and androgen therapy in patients with severe aplasia. Patients were not randomized to receive or not receive marrow infusion, since not all patients had suitable donors by the defined criteria. Placement of a subset of patients without donors into the "no-marrow" group would have obviated the randomness of entry into the two treatment groups. Since community-donor HLA-matched platelets were available to patients without family-member donors, comparable supportive care was available to both groups. Neither response rate nor survival was improved by the addition of the infusion of HLA-haploidentical marrow cells. These data thus corroborate the results of the Swiss study previously reported.1

Multivariate analysis identified two clinical parameters associated with a higher incidence of hematologic responses: a shorter duration of aplasia and a higher admission granulocyte count. Increased survival was correlated with these two factors, as well as with younger age at time of entry into the study. Although significant as independent variables, a shorter duration of aplasia and a higher granulocyte count both may identify patients who have had reversible stem cell injury and thus are capable of autologous recovery. A poorer prognosis among older patients may reflect a decreased ability to recover from acute insults, e.g., infections, which accounted for the majority of deaths. However, significance levels obtained throughout the analyses are based on asymptotic methods, and therefore should be interpreted with caution in light of the relatively small sample size.

The patients in this study who recovered after ATG therapy have had a varied course. In general, platelet counts recovered more slowly than reticulocyte or granulocyte counts, and usually the degree of recovery was incomplete. Total white blood counts tended to remain in the low normal range, although absolute granulocyte counts usually attained normal levels in patients with complete responses. Fluctuation of platelet counts was frequently seen without any change in therapy. Oscillation has been noted less frequently in white blood counts, and only rarely have red cell counts varied in the absence of any bleeding episode.

Relapse has now occurred in four patients. None of these patients had a "known" cause for aplasia, and they could have had repeated exposure to some extrinsic factor or a reactivation of an immune process. Since the dose of ATG given in this study was constant, inadequate or excessive therapy may have been received by some patients. Without a clear understanding of the mechanism of action of ATG in this setting, it was impossible to individualize therapy. Salvage of these patients after retreatment with ATG and/or androgen suggests that a similar type of biologic insult occurred during both episodes of aplasia.

The results of this study are superficially improved over those of our previous trial of 19 patients. Although complete and partial responses were similar in both studies (6 of 19 versus 21 of 53, \(\chi^2 = NS\)), 1-yr survival in the first trial was 42% compared to 68.5% in the current group \((p = 0.13\) by log-rank test). Patients in both studies had severe aplasia and were newly diagnosed. However, there were potentially important differences in the therapeutic regimens used. In the initial pilot study, ATG was administered over a shorter period of time (4 days versus 10 days), and no patient received androgen therapy. Firm conclusions from direct comparison of these two studies are thus not possible.

Several questions remain unanswered. Whether or not the addition of androgen therapy increases the frequency of recovery over that of ATG alone has not been studied in a randomized trial. The presumed mechanism of action of ATG in treating aplastic anemia, i.e., elimination of a population of suppressor T lymphocytes, is also unproven. The use of monoclonal anti-T-cell antibodies directed against suppres-
sor cells in place of the polyclonal ATG may be useful in testing this hypothesis.

Data from this study suggest that ATG should be given early in the course of severe aplasia. However, for those patients with HLA-compatible donors, results of marrow transplantation are best in the newly diagnosed untransfused patient. In Seattle, the long-term survival of untransfused patients with severe aplasia undergoing HLA-matched transplants is 82%. In general, older patients, for whom marrow transplantation is more hazardous, can be offered ATG early in the course of their disease. Patients who have only mismatched donors available may also be advised to consider ATG therapy first before incurring the present risks associated with a mismatched transplant. Ideally, if in vitro tests were available that predicted subsequent response to immunosuppressive therapy, patients at high risk for major morbidity from a marrow transplant might be advised to receive ATG therapy first.

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Therapy of severe aplastic anemia with anti-human thymocyte globulin and androgens: the effect of HLA-haploidentical marrow infusion

K Doney, SJ Dahlberg, D Monroe, R Storb, CD Buckner and ED Thomas