Long-Term Outcome of Aplastic Anemia in Adults Treated With Antithymocyte Globulin: Comparison With Bone Marrow Transplantation

By Ronald L. Paquette, Neyssan Tebyani, Margaret Frane, Priscilla Ireland, Winston G. Ho, Richard E. Champlin, and Stephen D. Nimer

The outcome of 155 adult aplastic anemia (AA) patients treated with antithymocyte globulin (ATG, Upjohn, Kalamazoo, MI) at University of California, Los Angeles from 1977 to 1988 was evaluated. The median survival of the 146 patients who did not undergo bone marrow transplantation was 5.6 years, with 49% ± 4% surviving more than 6 years. The most important predictor of survival was positive response to ATG (P < 0.001), which was observed in 48% of patients. Among pretreatment variables, disease severity was the best predictor of survival. Patients with moderate AA (MAA) had significantly better survival than those with severe (SAA) or very severe (VSAA) disease (P = 0.04). The 6-year actuarial survival rates of the three groups were 71% ± 9%, 48% ± 7% and 36% ± 7%, respectively. Cox regression analysis found disease severity to be the only pretreatment variable significantly associated with survival (P = .02). Patient age, sex, disease etiology, concurrent treatment with androgens, or duration of ATG therapy were not associated with differences in survival or response to ATG. Late clonal hematologic complications (ie, myelodysplasia, acute myelogenous leukemia) were observed in 5 of the 77 patients followed for more than 2 years after ATG treatment. In addition, one case of non-Hodgkin's lymphoma and three solid tumors occurred in the ATG-treated patients. The survival of 56 ATG-treated patients with SAA or VSAA between the ages of 16 and 43 did not differ significantly from that of 55 adult AA patients who underwent bone marrow transplant (BMT) during the same time period (P = 0.6). However, 6-year survival rates improved from 43% for patients transplanted before 1984, to 72% for those who underwent BMT between 1984 and 1989. In contrast, there was no difference in the survival rates of patients treated with ATG during these two time periods (46% ± 45%, respectively). The results suggest a superior long-term outcome for adult patients with SAA treated with BMT rather than with ATG alone, using current protocols.

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From the University of California, Los Angeles School of Medicine, Los Angeles, CA; St Joseph’s Hospital, Orange, CA; the M. D. Anderson Cancer Center, Houston, TX; and the Memorial Sloan-Kettering Cancer Center, New York, NY.

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Address reprint requests to Ronald L. Paquette, MD, Division of Hematology/Oncology University of California, Los Angeles Department of Medicine, 11-934 Factor Building, 10833 Le Conte Ave, Los Angeles, CA 90024-1678.

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for 4 additional weeks. One patient who relapsed after responding to ATG was treated with a murine monoclonal anti-T lymphocyte antibody conjugated to the ricin A chain (XomaZyme-H65; XOMA Corp, Berkeley, CA) 0.33 mg/kg intravenously daily for 10 days.

**Cytokine therapy.** Three patients who did not respond to ATG and two patients who relapsed after ATG therapy were treated with recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF; Sandoz Research Institute, East Hanover, NJ) at doses ranging from 4 to 64 μg/kg/d by continuous intravenous infusion, as previously described.15 One patient who relapsed after ATG treatment received recombinant human interleukin-3 (IL-3; Sandoz Research Institute) at doses of 5 and 10 μg/kg/d subcutaneously for 21 days.15

**Bone marrow transplantation.** Fifty-five adult patients with SAA or VSA underwent allogeneic BMT between October 1977 and November 1988. The clinical characteristics of these patients at presentation are detailed in Table 2. Previously untransfused patients (n = 4) were conditioned with cyclophosphamide (200 mg/kg) alone; all but one of the remaining patients received cyclophosphamide, followed by either total body irradiation (n = 36) or total lymphoid irradiation (n = 14) on day -1. Total body irradiation (300 cGy) was administered using a single 60Co source at 5 to 7 cGy/min.17 Total lymphoid irradiation was administered as a single dose of 300 cGy through anterior and posterior portals using 10 MeV X-rays.13 Graft versus host disease (GVHD) prophylaxis consisted of methotrexate alone15 in 37 patients and methotrexate plus cyclosporine20 in 18 patients.

**Statistical analysis.** All 155 patients who received ATG were evaluated for response to therapy, but only the 146 patients who did not subsequently undergo BMT were studied for survival. Variables examined in the survival analysis of ATG-treated patients included age, sex, etiology, duration of disease, disease severity, prior infectious or bleeding episodes, previous treatment with androgens or glucocorticoids, type of adjunctive treatment, and response to ATG.

**Table 1. Pretreatment Variables for Patients Who Received ATG Therapy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>16-45: 85 (65); 46-82: 70 (45)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male: 83 (54); Female: 72 (46)</td>
</tr>
<tr>
<td>Disease severity</td>
<td>Moderate: 30 (19); Severe: 70 (45); Very severe: 55 (30)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>&lt;15 days: 39 (25); 15-150 days: 76 (49); &gt;150 days: 40 (26)</td>
</tr>
<tr>
<td>Prior bleeding event</td>
<td>52 (34)</td>
</tr>
<tr>
<td>Prior infectious event</td>
<td>22 (14)</td>
</tr>
<tr>
<td>Etiology</td>
<td>Idiopathic: 113 (73); Drug: 24 (16); Hepatitis: 11 (7); Other: 7 (4)</td>
</tr>
<tr>
<td>Previous therapy</td>
<td>Glucocorticoids: 73 (47); Androgens: 56 (36); T101: 3 (2)</td>
</tr>
</tbody>
</table>

**Table 2. Comparison of Pretreatment Variables in Patients Receiving ATG or Undergoing BMT**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ATG (%)</th>
<th>BMT (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>16-19: 8 (15); 19-29: 20 (40); ≥30: 28 (45)</td>
<td>20 (36); 23 (42); 12 (22)</td>
<td>0.009</td>
</tr>
<tr>
<td>Sex</td>
<td>Female: 23 (41); Male: 33 (59)</td>
<td>19 (35); 36 (65)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration</td>
<td>≤30 days: 24 (43); &gt;30 days: 32 (57)</td>
<td>23 (42); 32 (58)</td>
<td>NS</td>
</tr>
<tr>
<td>Severity</td>
<td>Severe: 29 (52); Very severe: 27 (48)</td>
<td>34 (62); 21 (38)</td>
<td>NS</td>
</tr>
<tr>
<td>Prior infectious event</td>
<td>8 (14)</td>
<td>13 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>Prior bleeding event</td>
<td>23 (41)</td>
<td>37 (67)</td>
<td>0.008</td>
</tr>
<tr>
<td>Etiology</td>
<td>Idiopathic: 40 (74); Drug: 4 (7); Hepatitis: 8 (14); Other: 4 (7)</td>
<td>39 (71); 3 (5); 5 (9); 8 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous therapy</td>
<td>Glucocorticoids: 27 (48); Androgens: 27 (48)</td>
<td>24 (44); 16 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>ATG</td>
<td>0 (6)</td>
<td>3 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>T101</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Abbreviation:** NS, not significant.
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The duration of disease was divided into three levels: less than 15 days (the 25th percentile), 15 to 150 days, and more than 150 days (the 75th percentile). Age was separated into two levels: ≤45 years and >45 years. Response to ATG was represented by four levels: complete response, partial response, no response, or early death after ATG therapy, as predicted by the Kaplan and Meier product-limit method. Numbers in italics represent the patients at risk at the indicated duration of follow-up.

Variables used in the survival analyses for ATG- and BMT-treated patients included age, disease duration, disease severity, and prior bleeding or infectious episodes. Age was divided into three levels: ≤19, 20 to 29 and ≥30 years. The duration of disease was stratified as either ≤30 days or >30 days. Survival analyses were performed as above.

RESULTS

Survival after ATG. The median survival of 146 adult AA patients who did not undergo BMT was 5.6 years, and the actuarial survival rate at 6 years of follow-up was 49% ± 4%. Survival was significantly associated with disease severity at the time of treatment (P = .03; Fig 1). Patients with MAA had significantly longer survival times than patients with SAA or VSAA (P = .04); the outcomes of patients with SAA or VSAA were not significantly different. The 6-year actuarial survival rate of patients with MAA, SAA, and VSAA was 71% ± 9%, 48% ± 7% and 38% ± 7%, respectively. The duration of disease before treatment was also significantly associated with survival (P = .01). Patients with a time from diagnosis to treatment of 15 to 150 days had a superior survival rate compared with patients with disease durations of less than 15 days or more than 150 days. However, disease duration was significantly associated with severity (P = .04). Patients with VSAA were more than twice as likely to present within 15 days of diagnosis than those with less severe AA. Cox regression analysis showed that disease severity was the only pretreatment variable significantly associated with survival (P = .02).

Response to ATG was strongly associated with long-term survival (P < .001). Complete and partial responders had similar survival outcomes (Fig 2), with a combined 6-year actuarial survival of 83% ± 5%. Nonresponders had an actuarial 6-year survival rate of 20% ± 6%. Two courses of ATG or adjunctive treatment with androgens or cyclosporine did not significantly affect survival rates when compared with standard ATG treatment. Patient age, sex, disease etiology, prior bleeding or infectious episodes, or previous treat-

![Graph](https://www.bloodjournal.org)
with glucocorticoids or androgens did not significantly influence survival.

Response to ATG. Responses were observed in 74 (48%) of 155 adult patients treated with ATG including 19 complete and 55 partial responses. No response was seen in 60 patients and early death (<3 months after ATG administration) occurred in 21 patients. Although disease severity was significantly associated with response to ATG (P = .02), this was largely because of fewer early deaths (<3 months after treatment) in MAA (7%) or SAA (7%) than in VSAA (26%). After excluding those patients who died within 3 months of initiating therapy, response rates in MAA (54%) or SAA (57%) were not significantly higher than those in VSAA (54%), (P = .4). Response to ATG did not correlate with disease duration or etiology, prior bleeding or infectious episodes, previous treatment with androgens or glucocorticoids, or patient age or sex.

Late complications following ATG. Recurrent AA occurred in 8 of 74 responding patients, all of whom were partial responders. All relapses occurred within 3 years after ATG treatment; the 3-year actuarial relapse risk was 12% ± 4%. MDS and/or AML developed in 5 patients between 2.5 and 10.5 years after ATG therapy (median 4.1 years, Table 3). Thus, there was a 13% ± 7% actuarial risk of developing MDS or AML among long-term AA survivors. PNH was not clinically apparent in any late survivors, although systematic testing of patients was not performed following ATG therapy in the absence of suggestive clinical abnormalities. Various malignancies occurred in long-term survivors between 1 and 9 years following ATG therapy, including one case each of non-Hodgkin's lymphoma, hepatocellular carcinoma, squamous cell carcinoma of the lung, and prostate cancer. The actuarial risk of developing lymphoma or a solid tumor within 10 years after ATG treatment was 11% ± 6%. Two patients developed transfusion-associated AIDS.

Response to salvage therapy. Eighteen patients who did not respond to ATG were treated with alternative therapies (Table 4). Sustained hematologic improvement occurred only after repeat ATG therapy (1 of 2) or BMT (3 of 7). Inexplicably, two patients who received TP-1, a bovine thymus extract, gradually regained nearly normal peripheral blood counts beginning approximately 1 year after their last treatment. Among patients receiving transplants for persistent AA, two received HLA-matched marrow from unrelated donors. One patient has become a long-term survivor and the other died of transplant-related toxicity. Two of five patients who underwent allogeneic BMT survived.

All eight patients who relapsed after an initial response to ATG therapy received some form of salvage therapy (Table 5). Although a response was again achieved in 5 of 7 patients who were retreated with ATG, sustained hematologic improvement was observed in only 2 patients. In addition, 1 patient who experienced a bilineage response to interleukin-3 showed persistent hematologic improvement after withdrawal of the drug.

Survival after BMT. The survival rate of 55 adult SAA patients who underwent BMT between 1977 and 1989 was 52% ± 7% at 6 years. Graft rejection was observed in 5 patients (9%) and one patient died suddenly before en-
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graftment. Acute GVHD (grade ≥2) was observed in 19 of 32 engrafted patients (59%) who received methotrexate (MTX) prophylaxis and in 6 of 16 patients (38%) who were treated with cyclosporine (CsA) and MTX \( (P = .2) \). Chronic GVHD developed in 15 of 39 patients who survived at least 100 days, including 11 of 22 treated with MTX (50%) and 4 of 16 treated with CsA plus MTX (25%), \( (P = .2) \). Over time, there was improvement in outcome after BMT. The 6-year survival rate of patients treated before 1984 (who received MTX prophylaxis) was 43% compared with 72% in patients who underwent transplants from 1984 to 1989 (who received CsA and MTX; \( P = .08 \)). No clonal hematologic disorders or solid tumors developed in any patient who underwent BMT.

**Comparison of ATG and BMT.** Fifty-six AA patients between the ages of 16 and 43 years received ATG therapy for SAA or VSAA between October 1977 and November 1988. Survival of this subset of ATG-treated patients was compared with that of 55 patients in the same age range who underwent BMT during the same time period. The long-term outcome of these two groups was comparable \( (P = .8) \). However, significantly more patients in the youngest age group (16 to 19 years) underwent BMT compared with ATG treatment \( (P = .009) \) whereas significantly more older patients \( (≥30 \text{ years}) \) were treated with ATG than with BMT \( (P = .003) \). Therefore, the survival of three age groups was examined after ATG therapy or BMT. For each age group, there was no significant difference in long-term outcome based on the type of treatment administered. Additional stratifications based on disease duration or severity did not disclose any subgroup of patients who had superior survival rates with ATG treatment or BMT. BMT patients had a significantly higher incidence of prior bleeding episodes than did the ATG-treated patients but this variable was not prognostically important for either patient group.

Although the survival of SAA patients treated with ATG or BMT was similar, improvements in BMT methodologies have occurred over time. The administration of CsA as GVHD prophylaxis represented one major advance in transplantation, therefore, SAA patients who had BMT before, or after CsA administration was initiated were compared with SAA patients who were treated with ATG during the same time period (Fig 3). Patients who received MTX alone for GVHD prophylaxis, (those treated before 1984), had a very similar 6-year survival to patients treated with ATG during the same period of time (43% vs 46%, respectively; Fig 3A). In contrast, the 6-year survival of BMT patients who received CsA and MTX for GVHD prophylaxis (after 1983) was 72% compared with 45% for ATG-treated patients (Fig 3B). However, the differences in survival for the latter two groups did not reach statistical significance \( (P = .25) \).

**DISCUSSION**

The use of immunosuppressive therapy has dramatically improved the outlook for patients with AA. Spontaneous hematologic improvement occurs infrequently in AA, but 48% of adult AA patients treated at our institution responded to ATG therapy. The frequency of long-term survival (47%) was very similar to the ATG response rate, largely reflecting the poor outcome of nonresponders. Indeed, response to ATG was the most significant variable associated with long-term survival. Several early attempts to improve the outcome of ATG-treated patients were not successful. Repeated ad-
ministration of ATG did not improve response or survival rates in our study or in that of Young et al. The role of adjunctive treatments to standard ATG therapy is not yet clearly defined. A randomized placebo-controlled trial at UCLA showed no difference in response or survival rates between patients treated with ATG and androgens compared with those receiving ATG alone. Our long-term follow-up of the adult patients enrolled in that study shows no survival advantage in the androgen-treated group. A recent European study reported significantly higher response rates in 72 AA patients randomized to receive ATG and androgens compared with 68 patients treated with ATG alone. However, no survival advantage was observed in the patients treated with androgens. The combined use of CsA and ATG resulted in significantly improved response rates compared with ATG administration alone in a randomized study by the German Aplastic Anemia Group, but differences in survival were not observed between the treatment groups. Preliminary results reported by Rosenfeld et al support a potential benefit of using combined ATG and CsA therapy in the treatment of AA.

Disease severity was the only pretreatment variable that was independently associated with response to ATG and survival. British1 and European2 groups also have identified AA severity as an important prognostic variable. Disease severity most profoundly affected the incidence of early death, which was much higher in VSAA (26%) than in SAA (7%) or MAA (7%). After excluding patients who died within 3 months of ATG therapy, there were no significant differences in response or survival rates between the severity groups. This suggests that if patients with severe cytopenias could be supported during the interval after ATG treatment, their response and survival rates might approach those of patients with less severe AA.

Various late complications were observed in ATG-treated patients. Recurrent AA occurred in 12% of ATG responders, all within 3 years of treatment. Although relapsed patients usually responded to a second course of ATG, hematologic improvement persisted in only 29% of retreated individuals. Five of 77 patients who survived at least 2 years developed a clonal hematologic disorder including MDS or AML between 2.5 and 10.5 years after ATG therapy (actuarial incidence of 13% after 10.5 years). The frequency of these disorders is similar to that reported by several other centers. Doney et al7 found that MDS or AML developed in 5 of 124 patients followed for more than 100 days after ATG. De Planque et al observed 12 cases of MDS or AML in 223 AA patients who survived at least 2 years after administration of antilymphocyte globulin (ALG). A recent update by this group identified 31 cases of MDS or AML in 619 AA patients with at least 6 months of follow-up after ALG. The 10-year cumulative risk for MDS or AML was 9.6% and 6.6%, respectively, in that series. Speck et al reported that 10 of 111 SAA patients treated with ALG eventually developed MDS, in 5 of whom it evolved into AML. The frequency of PNH after immunosuppressive therapy for AA has varied widely among centers. We did not observe this complication and only one case was observed among 139 AA patients treated in Seattle. Speck and colleagues found that 18 of 111 AA patients developed PNH after ALG therapy, however all patients in this study were routinely tested for PNH at regular intervals and 6 of the 18 patients who were diagnosed with PNH were asymptomatic. Testing for PNH in our patients was performed only when the diagnosis was clinically suspected; thus, subclinical PNH after immunosuppressive therapy could occur more commonly than is recognized. However, laboratory evidence of PNH can be identified in up to 15% of patients who present with aplastic anemia. If red cell transfusions are administered before performing the sucrose hemolysis or Ham’s tests, the diagnosis of PNH may be obscured. Therefore, some patients found to have PNH at follow-up may have had this disorder before immunosuppressive therapy.

One case of non-Hodgkin’s lymphoma and three cases of solid tumors occurred after ATG therapy for an actuarial risk of 11% after 10 years. This is considerably higher than the one case of non-Hodgkin’s lymphoma and 7 cases of solid tumors (10-year actuarial incidence of 2.2%) observed after ALG in 860 patients reported by Socié et al. Clearly, AA survivors should be closely monitored for the development of solid tumors as well as clonal hematopoietic disorders.

The long-term survival of SAA or VSAA patients aged 16 to 43 years treated with ATG therapy or BMT between 1977 and 1989 was comparable. Two other groups have compared the outcomes of adult SAA patients who underwent immunosuppressive therapy or BMT. Doney et al reported that the long-term survival of SAA patients was equivalent after ATG therapy or BMT. Seven-year survival was significantly better for patients less than 16 years old who had BMT compared with those who had ATG therapy, whereas the outcome for adult patients was similar after either treatment. In contrast, the European BMT SAA Working Party found that patients greater than 20 years old who received ALG had significantly superior survival rates compared with those who underwent BMT. The predominant benefit of ALG was observed in patients with SAA; those with VSAA had similar outcomes after ALG or BMT. However, 22% of patients analyzed in the BMT arm who had previously received ALG and prior immunosuppressive therapy was associated with a poorer outcome in patients undergoing BMT. There was no significant difference in survival between previously untreated patients who received ALG therapy or BMT. Therefore, neither study showed any survival advantage for immunosuppressive therapy or BMT as primary treatment in adult AA patients.

Crump et al28 recently conducted a trial in which all adult SAA patients were initially treated with immunosuppressive therapy and only those who did not respond were considered for BMT. This strategy resulted in an 80% 5-year actuarial survival rate for 31 AA patients. Only five patients in our series underwent allogeneic BMT after not responding to ATG therapy, two of whom survived. It should be noted that 14 (25%) of 56 ATG-treated patients of transplant age died within 100 days of beginning ATG therapy. Early BMT, but not ATG therapy, can prevent early deaths in patients with severe pancytopenia, albeit at the risk of transplant-related morbidity and mortality. A clear disadvantage to the BMT salvage approach is the increased patient exposure to blood products. The International Bone Marrow Transplant Regis-
try (IBMTR) reported that SAA patients who received ≥20 transfusions before BMT had significantly reduced survival rates compared with those who received fewer than 20 transfusions, and untransfused SAA patients seem to have a particularly favorable outcome after BMT. Despite these shortcomings, the BMT salvage approach may be appropriate for patients with moderate AA or for a subset of SAA patients who are at increased risk for BMT-related complications.

There was a significant improvement in the outcome of BMT for SAA during the period of this analysis which was largely because of the use of CsA for GVHD prophylaxis. In our experience, comparison of patients who received MTX alone with those who were given MTX plus CsA showed a trend toward decreased acute GVHD (58% vs 38%) and chronic GVHD (50% vs 25%) associated with CsA administration. Six-year survival also favored patients receiving MTX plus CsA (72%) compared with those receiving only MTX (43%). The IBMTR reported that treatment including CsA, with or without MTX, when compared with treatment with MTX alone, was associated with significantly improved survival and decreased risk of chronic GVHD in SAA patients undergoing BMT. Changes in conditioning regimens for BMT may further improve survival. Preliminary results from a Seattle study using ATG and cyclophosphamide therapy before BMT resulted in a 2-year survival of 90%. Although the results of BMT for SAA have improved recently, we found no evidence that the outcome of patients treated with ATG had changed. Six-year survival of SAA patients who received ATG between 1977 and 1983 was similar to that of patients treated from 1984 to 1989, (46% vs 45%, respectively). Therefore the data suggests that allogeneic BMT currently offers a more favorable long-term outcome for adult SAA patients than does ATG therapy.

The use of immunosuppressive therapy and BMT has dramatically improved the survival of AA patients. Refinements in the use of these treatment modalities and supportive care will further enhance the long-term outlook for AA patients.

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Long-term outcome of aplastic anemia in adults treated with antithymocyte globulin: comparison with bone marrow transplantation

RL Paquette, N Tebyani, M Frane, P Ireland, WG Ho, RE Champlin and SD Nimer