Do Androgens Enhance the Response to Antithymocyte Globulin in Patients With Aplastic Anemia? A Prospective Randomized Trial


We analyzed the effect of antithymocyte globulin (ATG) with or without androgens in 121 patients with aplastic anemia. Fifty-three patients with moderate to severe aplastic anemia were prospectively randomized to receive ATG with or without oral androgens. Eleven of 26 patients (42%) receiving ATG plus androgen responded, including three complete and eight partial responses. Twelve of 27 patients (44%) receiving ATG plus placebo responded, including five complete and seven partial responses. The difference in response rates was not significant ($P > .9$). Survival was also comparable in the two groups: for patients with severe aplastic anemia, actuarial survival at two years was $55 \pm 24\%$ (95% confidence interval) in patients receiving ATG plus androgen compared with $50 \pm 24\%$ in the ATG plus placebo group ($P = .65$). Furthermore, results in both groups were indistinguishable from those obtained in 68 historical controls receiving ATG without androgens. These data indicate that androgens are not required in order to respond to antithymocyte globulin and the addition of androgens, as used in this trial, did not significantly improve response rates to ATG treatment.

A PLASTIC ANEMIA is a life-threatening hematologic disorder characterized by pancytopenia and an acellular or hypocellular bone marrow. It may occur following exposure to a large number of etiologic agents and result from a number of potential pathophysiologic mechanisms.1-3 Antithymocyte globulin (ATG) is an effective therapy for many patients with aplastic anemia, producing responses in 30% to 75% of patients.4-14 In a recent prospective randomized trial, we demonstrated a 50% partial or complete response rate to ATG treatment compared with no responses in untreated controls.4 These data were confirmed in an international collaborative trial.1 The mechanism whereby treatment with ATG improves bone marrow function in aplastic anemia is unknown. ATG may act to abrogate an abnormal immune-mediated suppression of bone marrow function or to favorably affect the basic regulation of hematopoiesis. Other mechanisms have also been suggested, including a direct stimulatory effect on hematopoietic stem cells or the activation of accessory cells.

Speck and co-workers,7,8 and others,9 have suggested that androgens enhance the response to antithymocyte globulin (ALG) or ATG therapy. This point is controversial, however. Androgens have only limited activity as single agents for aplastic anemia and have not proven effective for severe aplastic anemia in controlled trials.15,16 In previous studies at UCLA, 35 of 68 (51%) patients with aplastic anemia responded to ATG without androgens.17 Furthermore the addition of androgens to ALG did not increase the response rate in a retrospective analysis by the European Bone Marrow Transplant Group.14 In view of the well-established adverse effects of androgens,16,18,19 we sought to determine whether ATG plus androgens is superior to ATG alone for treatment of aplastic anemia in a prospective randomized trial.

MATERIALS AND METHODS

Patients with moderate or severe aplastic anemia were eligible for study entry. On-study criteria included an acellular or hypocellular bone marrow with less than 50% of normal cellularity and less than 5% myeloblasts. Severe aplastic anemia was defined by two or more of the following: granulocytes $<0.5 \times 10^9$ per liter, reticulocytes $\leq 40 \times 10^9$ per liter with hemoglobin $\leq 10 \text{g/dL}$, and platelets $\leq 20 \times 10^9$ per liter. Moderate aplastic anemia was defined by two or more of the following: granulocytes $<1.0 \times 10^9$ per liter, reticulocytes $\leq 60 \times 10^9$ per liter with hemoglobin $\leq 10 \text{g/dL}$, and platelets $<50 \times 10^9$ per liter. Patients with severe aplastic anemia who were under age 30 years were eligible only if they lacked an HLA-identical donor for bone marrow transplantation. Patients with Fanconi's anemia, nutritional deficiencies, cancer, or exposure to cytotoxic chemotherapeutic drugs or radiation were not eligible. Patients received antithymocyte globulin (ATGAM lot 17924 provided by the Upjohn Co, Kalamazoo, Mich) at a dose of 20 mg/kg/d for eight consecutive days. Patients were routinely premedicated with acetaminophen 650 mg orally and diphenhydramine, 50 mg intravenously. In patients developing chills, subsequent infusions were preceded by hydrocortisone 50 mg intravenously. All patients received prednisone, 40 mg/m$^2$/d orally beginning on day 8 to suppress the manifestations of serum sickness. The prednisone was tapered as tolerated and discontinued after one to two weeks. No patients received an infusion of bone marrow cells.

Randomization was stratified by the degree of pancytopenia (moderate or severe) and by the interval from diagnosis to study entry ($\leq$ or $> 6$ months). Patients in each stratum were randomized by the closed envelope technique to receive or not receive androgens. The first ten patients in this study received oxymetholone 4 mg/kg/d orally or no androgen. The subsequent 43 patients received coded oral tablets containing either fluorouracil, 25 mg/m$^2$/d, or placebo. The androgen/placebo tablets were begun on day 1 of the ATG therapy and continued for six months. Both the investigators and patients were blinded to the treatment assignment. The coded tablets were discontinued if the bilirubin was $>1.2$ mg/dL or alkaline phosphatase three times normal. Patient compliance in taking the study tablets was confirmed by direct communication and enumeration of remaining tablets in follow-up visits. The results of treatment for these two groups were also compared to those of 68 historical controls receiving ATG without androgens in previous UCLA studies.
Supportive care. All patients received ATG therapy at the UCLA Center for the Health Sciences or its affiliated hospitals. Patients referred from outside of the Los Angeles area were treated in part by their local referring physicians, who agreed to comply with the protocol recommendations for supportive care. Patients were treated as outpatients whenever possible but were hospitalized to receive ATG and to control major infections or bleeding. Packed red cells were transfused when symptoms of anemia developed or when the hemoglobin was ≤7 g/dL. Platelets obtained from random HLA-mismatched donors were transfused into patients with bleeding. Patients refractory to platelets from random donors received platelets from single related donors who were partially or fully matched for HLA antigens. Prophylactic platelet transfusions were given only to patients with platelets <20 × 10^9 per liter and a documented bleeding diathesis. Febrile patients (>38.5 °C) with peripheral blood granulocytes <1.0 × 10^9 per liter were immediately hospitalized and treated with parenteral broad-spectrum antibiotics, including amikacin (5 mg/kg of body weight every eight hours) or moxalactam (57.5 mg/kg every 12 hours) and either carbencillin (75 mg/kg every four hours) or pipercillin (40 mg/kg every four hours) given intravenously.20 Granulocyte transfusions were not administered.

Response criteria. Patients were assessed at three and six months following treatment for hematologic response by prospectively defined criteria.4 Criteria for a complete response included a sustained recovery of granulocytes >2.0 × 10^9 per liter, hemoglobin >12 g/dL, and platelets >120 × 10^9 per liter independent of any blood product transfusions documented on three or more occasions more than one week apart. Criteria for partial response include a sustained increment in granulocytes ≥0.5 × 10^9 per liter above baseline, an increment in platelets ≥30 × 10^9 per liter above baseline, or resolution of all red blood cell transfusion requirements. These criteria were established by analyzing features correlated with survival in our initial phase I/II studies involving ATG.1,4,17

Statistical considerations. Clinical features in each patient group were compared using Fisher’s exact test. Continuous variables were compared using the Mann-Whitney rank sum test.21 Actuarial survival was determined by the method of Kaplan and Meier22 with determinations of 95% confidence intervals (CI). Comparisons in survival between groups were made by the generalized Wilcoxon test.23

RESULTS

Fifty-three patients entered the study; 26 were randomized to ATG plus androgen and 27 to ATG plus placebo. Also analyzed are 68 consecutive historical controls who received ATG without androgens. The pretreatment characteristics of these three groups are listed in Table 1. The groups were comparable for all major clinical features and known prognostic factors; there were no statistically significant differences for age, etiology of aplastic anemia, interval from diagnosis to study entry, and pretreatment peripheral blood counts. Seventy-four percent of the patients had severe aplastic anemia and 26%, moderate aplastic anemia. The interval from diagnosis to ATG treatment was less than six months in 69% of patients. The median follow-up of the survivors is 18 months (range, five to 29 months) for the randomized patients and 52 months (29 to 83 months) for the historical controls.

Results of the study are summarized in Table 2. Of the 26 patients randomized to receive ATG plus androgen, there were three complete responses and eight partial responses; a total response rate of 42%. Of the 27 patients randomized to ATG plus placebo, there were five complete responses and seven partial responses; a total response rate of 44%. These differences in complete, partial, and total response rates are not significant (P > .70, P > .77, and P > .9, respectively). Sixty-eight historical controls who would have met the entry criteria of this study received ATG in an identical dose and schedule without androgens; 12 have had a complete response, and 23 a partial response—a total response rate of 51%.

The results were similar when the 41 patients with severe aplastic anemia were analyzed separately. Eight of 20 (40%) patients randomized to ATG plus androgen responded versus nine of 21 (43%) patients randomized to ATG plus placebo. This difference is not significant (P > .9). Of 49 historical controls with severe aplastic anemia, 25 (50%) responded to ATG without androgens. Among 12 patients with moderate aplastic anemia, three of six patients in both the ATG plus androgen and ATG plus placebo groups responded.

Survival of the three patient groups is shown in Fig 1. For patients with severe aplastic anemia, actuarial two-year survival was 55% (95% CI, 31% to 79%) for the 20 patients receiving ATG plus androgen compared to 50% (95% CI, 26% to 74%) for the 21 patients in the ATG plus placebo

<table>
<thead>
<tr>
<th>Table 1. Pretreatment Characteristics</th>
<th>ATG and Androgen</th>
<th>ATG and Placebo</th>
<th>ATG: Historical Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>27</td>
<td>68</td>
</tr>
<tr>
<td>Age*</td>
<td>41 (4 to 76)</td>
<td>39 (3 to 76)</td>
<td>31 (1 to 72)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>24</td>
<td>22</td>
<td>48</td>
</tr>
<tr>
<td>Drug/toxin</td>
<td>2</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Interval diagnosis to ATG*</td>
<td>81 (3 to 1,891)</td>
<td>54 (8 to 4,399)</td>
<td>147 (4 to 2,558)</td>
</tr>
<tr>
<td>Peripheral blood counts ×</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10⁹ per L WBC*</td>
<td>1.6 (0.3 to 6.5)</td>
<td>2.3 (0.1 to 4.8)</td>
<td>1.8 (0.2 to 5.0)</td>
</tr>
<tr>
<td>Granulocytes*</td>
<td>0.4 (0 to 4.4)</td>
<td>0.4 (0 to 3.3)</td>
<td>0.4 (0 to 3.8)</td>
</tr>
<tr>
<td>Lymphocytes*</td>
<td>0.9 (0.1 to 2.2)</td>
<td>1.3 (0 to 3.2)</td>
<td>1.3 (0.2 to 3.7)</td>
</tr>
<tr>
<td>Reticulocytes*</td>
<td>10.1 (0 to 80)</td>
<td>24.0 (0 to 27.5)</td>
<td>19.6 (0 to 224)</td>
</tr>
<tr>
<td>Platelets*</td>
<td>15 (2 to 218)</td>
<td>12 (2 to 100)</td>
<td>12 (3 to 245)</td>
</tr>
</tbody>
</table>

*Median (range).
In patients with moderate aplastic anemia, actuarial two-year survival was 63% (95% CI 50% to 76%) compared to 100% in those receiving ATG plus placebo and androgens. The actuarial two-year survival for the ATG plus androgen group was 56% (95% CI 40% to 72%). Patients with an interval from diagnosis to ATG treatment greater than six months; three of six patients randomized to ATG plus androgen and none of seven receiving ATG plus placebo responded. This difference is not significant (P = .08), although the small number of patients precludes critical analysis of these data. There was no difference in response rates between the two treatment groups if patients are stratified by age, sex, bone marrow cellularity, or etiology of aplastic anemia. Pretreatment peripheral blood counts were also not predictive of response.

The toxicity due to ATG was comparable in both groups including fever, chills, and an erythematous or urticarial rash during the ATG infusion and symptomatic serum sickness in all patients. Asymptomatic sinus bradycardia occurred in five patients. Six patients became hypertensive during the eight-day period of ATG infusion and required antihypertensive therapy. One patient developed grand mal seizures on day 5 of the treatment regimen; no etiology was identified, and the ATG was discontinued. All other patients received the full eight-day course of ATG.

Three of 26 patients receiving ATG plus androgen developed cholestatic jaundice, which resolved after discontinuation of the ATG study tablets. This was not observed in any of the 27 patients in the ATG plus placebo group. This difference in the rate of hepatic toxicity was not statistically significant (P = .11).

DISCUSSION

The results of ALG and ATG therapy for patients with aplastic anemia have been highly variable with 30% to 75% response rates at different centers. This variability may have been highly variable with 30% to 75% response rates at different centers. This variability may
result from patient selection, the heterogenous pathophysio-
logic mechanisms producing aplastic anemia, different
sources of ALG and ATG, different doses and schedules of
administration, and the possible use of additional drugs such
as androgens or corticosteroids.

The effects of androgens on hematopoiesis has been exten-
sively evaluated.\(^{16,24,25}\) Androgens enhance the responsive-
ness of erythroid progenitors to erythropoietin and may also
enhance the growth of pluripotent and committed granulo-
cyte/macrophage progenitors. Because of these properties,
treatment with androgens has been extensively evaluated for
patients with aplastic anemia. Despite encouraging results in
early uncontrolled trials, recent data indicate that androgens
have only limited efficacy in the treatment of aplastic
anemia. Androgens have not been beneficial for severe
aplastic anemia in several controlled trials.\(^{15}\) Some patients
do respond, however, particularly patients with mild to
moderate pancytopenia. Responding patients may remain
dependent on androgens to maintain adequate peripheral
blood counts.\(^{26,27}\) Androgen treatment may be associated
with adverse effects including virilization, fluid retention,
hyperlipidemia, acne, and more seriously, hepatic toxicity
with cholestatic jaundice, peliosis hepatitis, and rarely, hep-
toma.\(^{18,19}\)

In this double-blind prospective randomized controlled
trial, patients receiving ATG plus androgen (oxymetholone
or fluoxymesterone) had complete, partial, and overall
response rates similar to patients receiving ATG plus place-
bo. Survival was also comparable for the two groups. Also,
there was no advantage for the ATG plus androgen group
over historical controls receiving ATG alone. The addition of
androgens to ATG was not beneficial in any subset of
patients, including those with severe or moderate aplastic
anemia, in patients with an interval from diagnosis of
aplastic anemia to treatment less than or greater than six
months, or in patients less than or greater than 40 years of
age.

The relatively small sample size limited the power of this
analysis. Given the sample of 53 randomized patients, there
was a 60% chance of detecting a 25% improvement in
response rates relative to the controls with \(\alpha = 0.10.\)
Although no benefit was detected in this study, it is possible
that a much larger study could detect a therapeutic advan-
tage for the addition of androgens to ATG. Subgroups of
patients with aplastic anemia may also exist in whom addi-
tion of androgens may be beneficial.

In conclusion, these data indicate that androgens are not
required for a response to ATG therapy and there was no
detectable benefit from combining androgens as used in this
study with antithymocyte globulin. In view of their potential
toxicity, androgen drugs should not be routinely combined
with ATG for treatment of aplastic anemia.

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REFERENCES

1. Gale RP, Champlin RE, Feig SA, Fitchen JH: Aplastic
2. Camitta BM, Storb R, Thomas ED: Aplastic anemia: Patho-
    1982
3. Thomas ED, Storb R: Acquired severe aplastic anemia: Prog-
    ress and perplexity. Blood 64:325, 1984
4. Champlin R, Ho W, Gale RP: Antithymocyte globulin treat-
    ment in patients with aplastic anemia: A prospective randomized
5. Camitta B, O’Reilly RJ, Sensenbrenner L, Rappoport J,
    Champlin R, Doney K, August C, Hoffmann RG, Kirkpatrick D,
    Stuart R, Santos G, Parkman R, Gale RP, Storb R, Nathan D:
    Antithoracic duct lymphocyte globulin therapy of severe aplastic
6. Mathe G, Schwarzenberg L: Treatment of bone marrow
    aplasia by bone marrow graft after conditioning with antilympho-
7. Speck B, Gluckman E, Haak HL, van Rood JJ: Treatment of
    aplastic anemia by antilymphocyte globulin with and without allo-
    aplastic anemia with antilymphocyte globulin or bone marrow
    Boiron M, Bernard J: Treatment of severe aplastic anemia with
10. Doney K, Dahlberg SJ, Monroe D, Storb R, Buckner CD,
    Thomas ED: Therapy of severe aplastic anemia with antihuman
    thymocyte globulin and androgens: The effect of HLA-haploidenti-
11. Rothman SA, Streeter RR, Bukowski RM, Hewlett JS:
    Treatment of severe aplastic anemia with antithymocyte globulin.
    Exp Hematol 10:809, 1982
12. Fairhead SM, Chipping PM, Gordon-Smith EC: Treatment
    of aplastic anemia with antithymocyte globulin (ALG). Br J
    Haematol 55:7, 1983
13. Miller WJ, Branda RF, Flynn PJ, Howe RB, Ramsay NKC,
    Condie RM, Jacob HS: Antithymocyte globulin treatment of severe
14. Gluckman E, Devergie A, Poros A, Degauqlet P: Results of
    immunosuppression in 170 cases of severe aplastic anemia: Report
    of the European Group of Bone Marrow Transplant. Br J Haematol
    51:541, 1982
15. Camitta BM, Thomas ED, Nathan DG, Gale RP, Kopecky
    KJ, Rappoport JR, Santos G, Gordon Smith EC, Storb R: A
    prospective study of androgens and bone marrow transplantation for
    289:72, 1973
17. Champlin R, Ho WG, Bayever E, Winston DJ, Lenarsky C,
    Feig S, Gale RP: Treatment of aplastic anemia: Results with bone
    marrow transplantation, antithymocyte globulin and a monoclonal
    anti T cell antibody, in Young NS, Humphries K, Levine A (eds):
    Aplastic Anemia: Stem Cell Biology and Advances in Treatment.
    New York, Alan R. Liss, 1984, p 227
    with oral androgen therapy. Arch Pathol Lab Med 101:405, 1977
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