RAPID COMMUNICATION

Intensive Immunosuppression With Antithymocyte Globulin and Cyclosporine as Treatment for Severe Acquired Aplastic Anemia

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Immunosuppressive therapy can produce hematologic improvement in a large proportion of patients with severe aplastic anemia. Antithymocyte globulin (ATG) is the current treatment of choice for patients who do not have histocompatible sibling donors or who are otherwise ineligible for allogeneic bone marrow transplantation. About 50% of patients respond to an initial course of ATG, and many nonresponders can be salvaged by subsequent treatment with cyclosporine (CsA). To determine whether simultaneous administration of these agents could further improve response rates, we enrolled 55 patients in a therapeutic trial of 4 days of ATG and 6 months of CsA. Among the 51 patients who had not received previous courses of ATG or CsA, 67% had responded by 3 months, and 78% had responded by 1 year (response was defined as an increase in peripheral blood counts sufficient that a patient no longer met the criteria for severe disease). There was a high incidence of relapse (36% actuarial risk at 2 years), but most relapsed patients responded to additional courses of immunosuppression, and relapse was not associated with a significant survival disadvantage. Evolution to myelodysplastic syndromes and acute leukemia was rare (1 of 51 patients), but the later appearance of paroxysmal nocturnal hemoglobinuria was more common (5 of 51 patients). Actuarial survival was 86% at 1 year and 72% at 2 years. These data support the use of a combination immunosuppressive regimen containing both ATG and CsA as first-line therapy for severe aplastic anemia.

APLASTIC ANEMIA is a rare disease characterized by pancytopenia and a hypocellular bone marrow (BM).[1] Allogeneic BM transplantation (BMT) can cure the majority of transplanted patients,[2] but most patients are ineligible for this procedure because they have no histocompatible sibling donor or because of age restrictions. Immunosuppression can achieve similar response rates to BMT,[3] and studies comparing these two treatment strategies have shown equivalent long-term survival.[4-7] The ideal immunosuppressive regimen would combine low toxicity with a high response rate and low risk of relapse of late complication. Currently, antithymocyte globulin (ATG) or antilymphocyte globulin (ALG), preparations of equine antisera raised against human thymocytes or thoracic duct lymphocytes, respectively, are used as first-line therapy, combined with steroids to minimize serum sickness. ATG is the only preparation commercially available in the United States. Therapy with these agents can result in response rates of up to 50%.[8,9] About half of nonresponders to an initial course of ATG/ALG can be salvaged with cyclosporine (CsA).[10,11] Additional regimens containing androgens, growth factors, and high-dose steroids have shown inconsistent results.[12-15] The combination of ALG, CsA, and high-dose corticosteroids was shown to have increased efficacy in severe aplastic anemia by the German Multicenter Trial when compared with the same regimen given without CsA,[16] but similar studies have not been done with ATG. In addition, the role of high-dose steroids in such a combination remains questionable. We now report a single center study of 55 patients with severe aplastic anemia treated with simultaneous administration of ATG and CsA, with steroids used at conventional doses to treat serum sickness.

MATERIALS AND METHODS

Patient selection. All patients referred to the Clinical Center of the National Institutes of Health (Bethesda, MD) with the diagnosis of aplastic anemia between December 1989 and February 1994 were evaluated for inclusion in the protocol. Only patients with severe disease were eligible. Severe disease was defined as BM cellularity less than 30% combined with two of the following three laboratory abnormalities: absolute neutrophil count (ANC) less than 500/mm^3, platelet count less than 20,000/mm^3, and reticulocyte count less than 40,000/mm^3. After January 1993, the inclusion reticulocyte count was raised to 60,000/mm^3 to reflect changes in assay instrumentation and maintain the same biologic value. The experimental nature of the protocol was explained, and all patients were required to give informed consent before treatment.

Exclusion criteria included a serum creatinine of greater than 2.0 mg/dL, underlying carcinoma or a history of recent radiation or chemotherapy, inability to comprehend the investigational nature of the study, and clinical status so grave that death within 7 to 10 days was likely. Women of childbearing age were excluded if they were pregnant or unwilling to use oral contraceptives. Patients were not excluded if they had received ATG or cyclosporine before the current study. There were no age limits, but patients had to weigh more than 10 kg. Patients were not excluded if they had active infections, or if their Ham's test for paroxysmal nocturnal hemoglobinuria was positive.

The protocol was approved by the Institutional Review Board of the National Heart, Lung and Blood Institute, National Institutes of Health (NIH).

Treatment plan. All patients were tested for sensitivity to ATG by subcutaneous administration of a test dose and underwent desensitization if the skin test was positive.[17] Equine ATG (Upjohn, Kalamazoo, MI) was administered in 500 mL of normal saline at a dose of 40 mg/kg/d over 4 hours on days 1 through 4, whenever possible through a central venous catheter. The administration rate was

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Table 1. Presentation Characteristics and Three-Month Response Rates in Patients and Historic Controls

	Patients	Historic Controls	*P* Value
No.	51	70	
Age	29.2 (3.6-79.4)	24.5 (1.0-76.8)	NS
Sex (M/F)	31/20	40/30	NS
Time before protocol therapy (d)	31 (6-483)	54 (3-6,398)	NS
Dates treated	12/89-2/94	9/81-11/89	
Presentation ANC	336 (0-1,800)	314 (0-1,980)	NS
Presentation absolute reticulocyte count	12,630 (0-63,080)	6,075 (0-149,500)	≈.007
Presentation platelet count	9 (1-57)	9 (1-92)	NS
Response	34 (67%)	20 (29%)	≈.0001
Death	3 (6%)	14 (20%)	≈.028

Values for presentation characteristics are given as median and range where applicable; values for outcomes are given as number of patients and percentage.

slowed if patients developed high fever or severe chills, but dose was not reduced.

CsA was begun on day 1 at an initial dose of 12 mg/kg/d in adults or 15 mg/kg/d in children, administered as an oral dose given twice daily. This initial dose was continued for 14 days, after which the CsA dose was adjusted to maintain a level between 200 and 400 ng/mL by radioimmunoassay. CsA was discontinued without a taper when patients returned to NIH for their 6-month evaluation.

Methylprednisolone was administered at a dose of 1 mg/kg/d or 40 mg/d, whichever dose was higher, beginning on day 1. For the first 4 days of treatment, 40 mg of methylprednisolone was mixed with the ATG and the remainder of the dose was given orally. After day 4, patients were switched to oral administration. This dose was continued until day 10 or until symptoms of serum sickness had resolved, and then rapidly reduced over approximately 2 weeks.

Table 2. Exposure History

Condition	No. of Patients
Idiopathic	39 (71%)*
Chemicals	
organophosphates	1
paint	1
unspecified	2*
Drugs	
sulfa	3
ibuprofen	1
unspecified	1
Pregnancy	3*
Hepatitis	1
Viral syndrome	1
Radiation	1
Trisomy 21	1
Total with exposure history	16 (29%)

*Patients who received at least one course of ATG and/or CsA before entering the present study. One such patient had no identified exposure, one an unspecified chemical exposure, and two developed aplastic anemia associated with pregnancy.

Table 3. Prior Therapy

Condition	No. of Patients
No prior therapy	23
Immunosuppression	
ATG	4
CsA	2
Total patients	4
Glucocorticoids	19
Androgens	8
Vitamins	
B12	3
Pyridoxine	2
Folate	3
Unspecified	1
Total patients	6
Growth factors	
GM-CSF	5
G-CSF	5
Erythropoietin	3
IL-1	1
Total patients	12
Intravenous Ig	4
Iron	1
Splenectomy	1
Vincristine	1

Patients enrolled after September 1991, were additionally given granulocyte colony-stimulating factor (G-CSF) for episodes of febrile neutropenia that did not respond to antibiotics. To receive G-CSF they had to meet the following criteria: ANC less than 500/mm^3, fever for greater than 48 hours despite adequate antibacterial and antifungal therapy, or a localized infection that increased in extent or severity despite adequate antimicrobial or antifungal therapy. The dose of G-CSF was 5 μg/kg/d that could be adjusted upward to 10 μg/kg/d if patients did not respond.

Clinical and laboratory studies. All patients were admitted to the Clinical Center for initial evaluation, including a history and physical exam, complete blood counts obtained on two separate occasions at least 24 hours apart, a BM biopsy and aspirate, B12, folate, iron studies, and a Ham's test for paroxysmal nocturnal hemoglobinuria. BM or peripheral blood cytogenetics were performed for patients with a history compatible with a myelodysplastic syndrome. Patients younger than 35 years of age with potential sibling donors had HLA typing if this test had not been performed before admission. A chromosome fragility assay using diepoxybutane stimulation was performed on all patients under 35 years or with a history compatible with Fanconi's anemia.

Patients were hospitalized until they were no longer at risk for serum sickness and were clinically stable. They returned for interval evaluations at 3 months, 6 months, 1 year, and then yearly or as clinically indicated. Periodic evaluations included a history and physical exam, complete blood count, Ham's test, and tests of renal and hepatic function.

Patients visited their local physicians for blood counts, serum blood urea nitrogen and creatinine, and liver function tests every week for the first month of therapy and then every 2 weeks. CsA dose was adjusted for signs of renal or hepatic toxicity. Blood samples for cyclosporine levels were collected every 2 weeks and sent to a single laboratory (Nichols Institute, San Juan Capistrano, CA) for analysis by radioimmunoassay. After 6 months, blood counts and chemistries were obtained as clinically indicated.

Supportive care. Packed red blood cell (RBC) transfusions were administered to maintain hemoglobin above 9 g/dL. Platelets were

Table 4. Outcomes at 3, 6, and 12 Months

	All Patients	Patients Who Did not Receive Prior Courses of ATG or CsA
Days of follow-up	994 (218-1714)	912 (218-1714)
Number evaluable		
3 mo	55	51
6 mo	55	51
12 mo	43	40
Responses		
3 mo	36 (65%)	34 (67%)
6 mo	38 (69%)	36 (71%)
12 mo	32 (74%)	31 (78%)
Deaths		
3 mo	4 (7%)	3 (6%)
6 mo	5 (9%)	5 (10%)
12 mo	5 (12%)	4 (10%)
Relapses		
6 mo	2 (5%)	2 (6%)
12 mo	8 (25%)	8 (26%)
PNH		
3 mo	3 (5%)	2 (4%)
6 mo	5 (9%)	4 (8%)
12 mo	4 (9%)	3 (8%)

Values are given as number, followed by rate as a percentage. Relapse rates are given as percentage of responders, rather than percentage of evaluable patients. Days of follow-up are given as median and range. There were no significant differences between any of the groups.

transfused to maintain a platelet count at greater than 20,000/mm^3 while patients received ATG, and at greater than 5,000/mm^3 at other times. Patients who were refractory to platelet transfusions did not receive platelets except while receiving ATG or during major bleeding episodes.

Parenteral broad-spectrum antibiotics were used to treat fevers during neutropenia. Although the choice of antibiotic was left to the clinical team caring for the patient, in most cases the first-line choice was monotherapy with ceftazidime. Amphotericin B was administered to patients who remained febrile for more than 7 days without an obvious bacterial source, or in whom a fungal etiology was suspected or documented at presentation with fever.

Aerosolized pentamidine at a dose of 300 mg every 4 weeks was used for prophylaxis against *Pneumocystis carinii* while patients were receiving cyclosporine.

Response definition. Patients were classified as responders if they met two of the following three criteria: ANC greater than 500/mm^3; platelet count greater than 20,000/mm^3; and reticulocyte count greater than 40,000/mm^3 (60,000/mm^3 after January 1993).

Data analysis. Actuarial survival was calculated using the method of Kaplan and Meier. All data were analyzed for significance using resampling techniques.[18] A minimum of 1,000 iterations was used for each test, and 10,000 iterations were used to confirm significance. Comparisons of survival curves and medians were performed without replacement.

Historical controls were collected from severe aplastic anemia patients enrolled in an earlier NIH protocol for treatment with ATG alone.

RESULTS

Patient characteristics. Fifty-five patients entered the protocol. The median age was 28 years, but the age distribution was biphasic, with a major peak in adolescence and a minor peak in the early 60s. The male to female ratio was 1.4:1. Most patients were referred soon after diagnosis, and the median delay between diagnosis and the first day of ATG was 31 days. The median neutrophil count at time of referral was 336/mm^3, the median platelet count was 9,000/mm^3, and the median absolute reticulocyte count was 12,960/mm^3 (Table 1).

The majority of patients had no identifiable exposure history (Table 2). Sixteen had been exposed to a variety of factors that have been associated with aplastic anemia, including three patients with onset during or shortly after pregnancy and one case of posthepatitis aplastic anemia.

Most patients were treated with more than supportive care before their inclusion in the current protocol (Table 3). Four patients had failed previous courses of ATG, CsA, or both given sequentially. A large number of patients had been treated with glucocorticoids, typically with several weeks of prednisone at a dose of at least 1 mg/kg/d. Eight patients had received short courses of androgens, and others received B12, pyridoxine, or folate, alone or in combination. Twelve patients were treated with growth factors, including granulocyte-macrophage CSF (GM-CSF), G-CSF, interleukin-1 (IL-1), and erythropoietin, usually for only a few days or weeks.

CsA toxicity. More than half of patients developed significant hypertension requiring treatment. Three patients had seizures, possibly associated with hypomagnesemia; in all three patients CsA was successfully restarted at target levels without seizure recurrence after initiating antiseizure medication. Three patients developed gynecomastia. Gingival hyperplasia was common, as were gastrointestinal symptoms, but in no case was CsA discontinued.

Outcome and survival. Outcomes were tabulated for all patients, for the 51 patients who had not received previous courses of ATG or CsA, and for the 4 patients who had received these drugs (Table 4). There were no significant

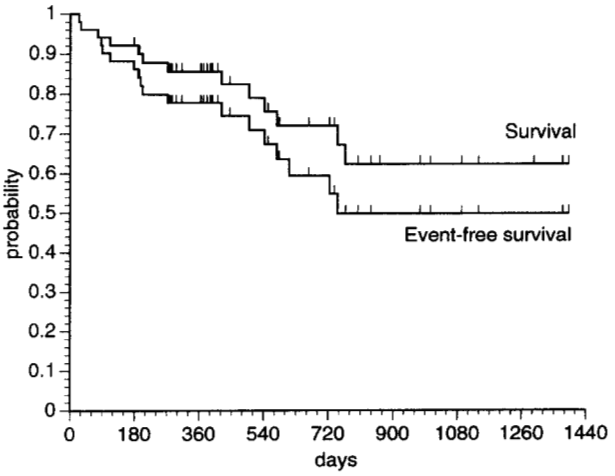

Fig 1. Survival and event-free survival. The four patients who had received previous courses of ATG and/or CsA are not included. Events included death or evolution to a clonal BM disorder.

Table 5. Outcomes by Previously Reported Prognostic Groups: ANC ≤200/mm³ and Age Less Than 20

	ANC ≤200/mm³	ANC >200/mm³	Age <20	Age >20
Days of follow-up	779 (252-1,714)	1064 (218-1,707)	969 (378-1,714)	912 (218-1,707)
No. evaluable				
3 mo	21	30	16	35
6 mo	21	30	16	35
12 mo	16	23	14	25
Responses				
3 mo	12 (57%)	22 (73%)	12 (75%)	22 (63%)
6 mo	13 (62%)	23 (77%)	13 (81%)	23 (66%)
12 mo	13 (81%)	17 (74%)	12 (86%)	18 (72%)
Deaths				
3 mo	2 (10%)	1 (3%)	0	3 (9%)
6 mo	3 (14%)	1 (3%)	0	4 (11%)
12 mo	2 (13%)	2 (9%)	1 (7%)	3 (12%)
Relapses				
6 mo	0	2 (9%)	1 (8%)	1 (4%)
12 mo	1 (8%)	7 (41%)	1 (8%)	7 (39%)
PNH				
3 mo	1 (5%)	1 (3%)	0	2 (6%)
6 mo	2 (10%)	2 (7%)	0	4 (11%)
12 mo	2 (13%)	1 (4%)	0	3 (12%)

Values are given as number, followed by rate as a percentage. Relapse rates are given as percentage of responders, rather than percentage of evaluable patients. Follow-up times are given as median and range. The only significant difference between the two ANC groups was in 12-month relapse rates ($P \approx .045$). None of the age differences reached significance.

outcome differences between these groups, and further analyses only included the 51 patients who had not received previous immunosuppressive therapy.

Response rates were 67% at 3 months, 71% at 6 months, and 78% at 12 months. However, by 12 months, 26% of responders had relapsed. Mortality was 10% at 1 year. The only evolution to clonal disease that occurred during the first year was the development of paroxysmal nocturnal hemoglobinuria (PNH), which occurred in 8% of patients by 12 months; these five patients all had experienced a hematologic response to treatment. Two had a positive Ham's test at the time a response was first documented, and appear to have evolved out of severe aplastic anemia rather than out of remission; the remaining three patients either had technically inadequate Ham's tests or failed to be tested at earlier times in remission. One patient developed acute myelogenous leukemia associated with monosomy 7 and died while undergoing unrelated BMT, more than 2 years after initial presentation.

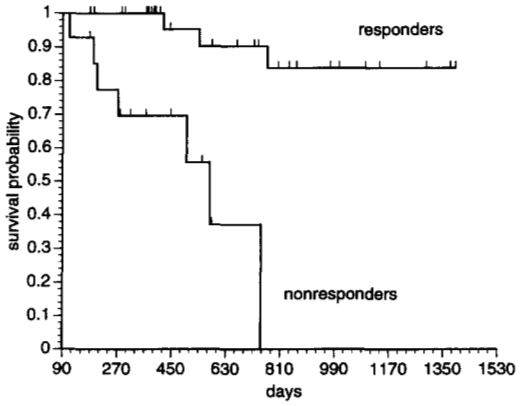

Fig 2. Survival of patients classified by response at 3 months. Patients who died before their 3-month evaluation, or who had received previous courses of ATG and/or CsA, are not included.

The three patients who died before their 3-month evaluation had fungal infections, although in one case this was a clinical diagnosis. Two patients died late of aspergillosis, one on day 191 and one on day 549; this latter patient had responded initially, but relapsed by 12 months; none of the other four patients had responded. Four patients underwent unrelated BMT at times ranging from day 112 to day 767, but none survived the procedure.

Actuarial survival at 1 year was 86%, falling to 72% and 62% at 2 and 3 years, respectively (Fig 1). Event-free survival was 78%, 59%, and 50% at 1, 2, and 3 years; events included in the analysis were death or evolution to a clonal BM disorder.

Presentation ANC less than 200/mm³ and age less than 20 years have both been reported to be poor prognostic factors in severe aplastic anemia,[7,9,16,19] especially in patients treated with immunosuppression. Although there was a trend toward lower rates of early response and higher mortality in patients with a low presentation ANC, neither factor was associated with a significantly poorer outcome (Table 5). In contrast, there was a trend toward better response in younger patients. The only difference that reached statistical significance was a higher relapse rate among patients with higher ANCs at presentation. There was a similar trend that did not reach significance for higher relapse rates among older patients.

Quality of response. We chose to define response strictly based on changes in objective hematologic parameters to

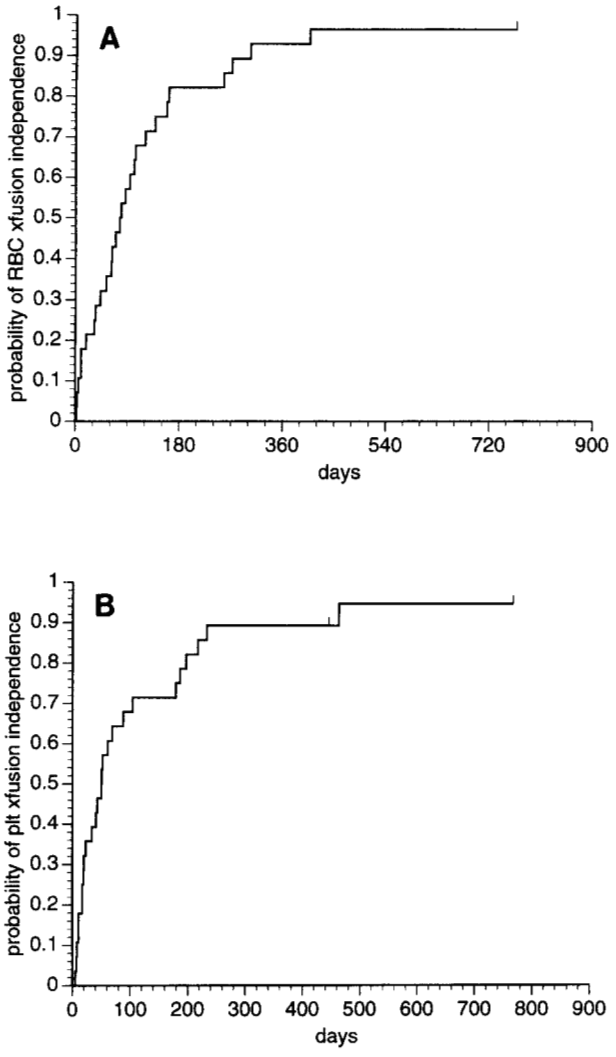

Fig 3. Transfusion-independence of responders who did not relapse. (A) shows the probability of RBC transfusion-independence with time. (B) shows the probability of platelet transfusion-independence with time.

avoid bias in individual clinical assessments and because transfusion policies varied with the patients' local physician. Response by this definition was highly correlated with survival (Fig 2). Actuarial survival at 1 year was 100% in responders and 70% in nonresponders ($P \approx .002$), and by 2 years, the rates had further diverged to 90% and 37%, respectively ($P \approx .003$).

Transfusion independence also correlated well with response (Fig 3). In responders who did not relapse, the actuarial probability of RBC transfusion independence was 93% at 1 year and 96% at 2 years. The probability of platelet transfusion independence was 89% at 1 year and 95% at 2 years. No nonresponder became transfusion independent, and no responder maintained transfusion independence despite hematologic relapse.

Improvements in ANC occurred in both responders and nonresponders (Fig 4). The data for nonresponders is biased toward improvement because patients whose neutrophil count did not improve are likely to have had a higher mortality, and deaths are censored from analysis. No responders died before one year. Responders had a sustained increment in both platelet count and absolute neutrophil count (Table 6).

Relapse. In patients who responded, the risk of relapse was 18% at 1 year and 36% at 2 years (Fig 5). No responders relapsed after 2 years. However, relapse was not associated with a significant decrease in actuarial survival (Fig 6). Survival of both relapsed and nonrelapsed responders was 100% at 1 year, falling to 75% and 100% at 2 years and 75% and 90% at 3 years. These differences represent only three deaths, two among relapsed patients and one in a patient in continuous response. Six of the ten relapsed patients responded to additional courses of immunosuppression with CsA alone or combined with ATG. Of the remaining four, one died after failing multiple additional courses of immunosuppression, one died before receiving any salvage therapy, one is currently being retreated with CsA and is too early in his course to evaluate, and one failed salvage therapy with androgens, but has not been retreated with immunosuppression.

Previously treated patients. Four patients were treated after having received earlier courses of ATG and CsA. Three had never responded, and one had responded and subsequently relapsed. Outcome rates in these patients were not significantly different from those of patients receiving their first course of immunosuppression, although the size of the group is too small to draw any meaningful conclusions. Two patients responded, although one evolved to PNH and the other continued to require infrequent platelet and RBC transfusions. This last patient elected to undergo unrelated BMT. One patient died before his 3-month evaluation, and the last patient is alive but still severely affected 3 years after receiving ATG/CsA.

G-CSF. Three patients received courses of G-CSF of 9, 33, and 50 days. In all cases, G-CSF was begun within the first month of the protocol. The patient who received 9 days responded by 3 months, the patient who received 33 days did not respond, and the patient who received 50 days never responded and died on protocol day 203.

Historical controls. Historical controls were selected from a group of patients with severe aplastic anemia who received a regimen of ATG without CsA on an earlier NIH protocol. All patients who met the inclusion criteria for the current trial were selected. There were no significant differences in the demographics of patients and controls. The absolute reticulocyte count at presentation was significantly lower in the controls, probably secondary to the evolution of methods for enumerating reticulocytes from supravital staining through two generations of automated counters.

Outcomes could only be compared at 3 months because of differences in protocol design and data collection. To compare response rates, the primary data for the historical controls was reviewed and the current response criteria were applied. The response rate at 3 months has more than doubled, whereas mortality has fallen significantly. Improvement in early response certainly contributed to the lower

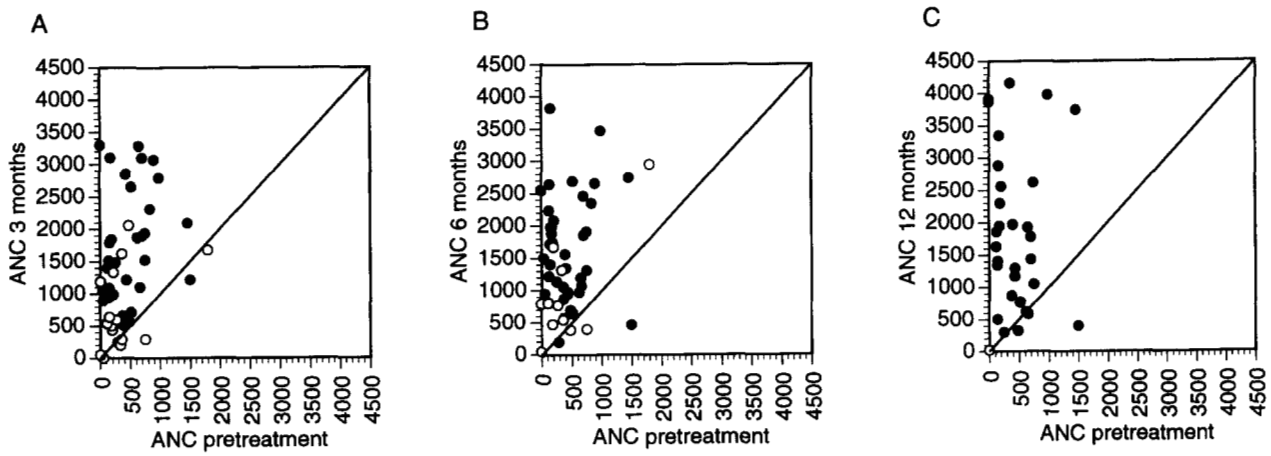

Fig 4. Changes in ANC with time. Filled circles represent responders and open circles nonresponders. (A) shows the changes at 3 months, (B), the changes at 6 months, and (C), the changes at 12 months. Points above the diagonal line represent improvement in ANC, whereas points below the line represent deterioration. Deaths are not included, and the data are biased toward improvement. The four patients who had received previous courses of ATG and/or CsA are not included.

mortality, but it is impossible to exclude contributions from improved supportive care, including the use of broad spectrum cephalosporins and early treatment with amphotericin B.

DISCUSSION

Our results confirm the superiority of aggressive combination immunosuppressive therapy as initial therapy for severe aplastic anemia. We achieved these results using a short course of ATG without high-dose methylprednisolone. In the German Multicenter Trial, ALG was given over 8 days; the shorter course of heterologous serum administration may decrease the incidence of serum sickness and possibly lead to shorter hospitalizations at lower cost. High-dose methylprednisolone (5 mg/kg/d) has been associated with an increased incidence of complications, especially avascular necrosis,[20] and does not appear necessary to achieve high response rates.[12]

We chose conservative response criteria based only on increases in absolute reticulocyte count, platelet count, and ANC. The peripheral blood counts of most of our patients did not return to normal range, and we chose not to differentiate between partial and complete responders. Such limited criteria risk missclassifying patients who have transient increases in peripheral counts, but who never achieve a clinically meaningful response. On the other hand, a patient who continues to be transfusion dependent for RBCs may have a meaningful, if incomplete, response, if their ANC increases sufficiently to protect them from life-threatening infection or if their platelet count increases enough to protect them from serious bleeding. Almost all of our responders who did not relapse reached transfusion-independence for platelets and RBCs. To further support the utility of our response criteria, response was highly correlated with both 1- and 2-year survival.

Only one of our patients evolved to acute leukemia or a myelodysplastic syndrome, a rate lower than reported in other studies.[12,21-23] Over 10% of patients developed PNH. All patients who evolved met our hematologic response criteria, although the patient who later developed acute leuke-

Table 6. Changes in ANC and Platelet Count With Response

	Median and Range
Change in ANC (mm^{-3})	
3 mo	1096 (−285 to 3300)
6 mo	1221 (−1,032 to 3,672)
12 mo	1262 (−1,100 to 3,910)
Change in platelet count ($10^3/mm^3$)	
3 mo	48 (−8 to 323)
6 mo	71 (−5 to 217)
12 mo	60 (−1 to 227)

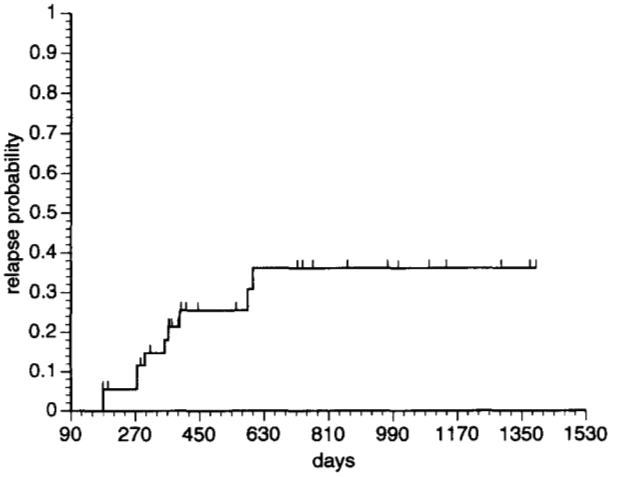

Fig 5. Probability of relapse in responders who had not received previous courses of ATG and/or CsA.

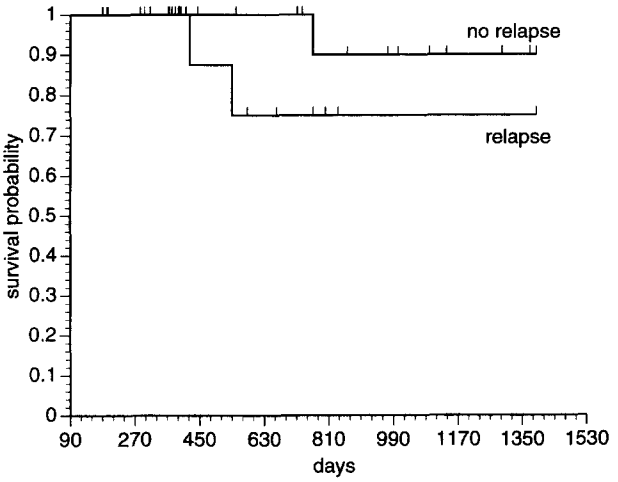

Fig 6. Survival of responders who relapsed compared with survival of patients with a sustained response. The four patients who had received previous courses of ATG and/or CsA are not included.

mia never achieved transfusion-independence, and one patient with PNH continued to require transfusions to support her hemoglobin. All patients had a negative Ham's test at initial evaluation, but all had been transfused. No patient who developed PNH had a clearly negative Ham's test between the time of response and diagnosis with PNH, so we could not determine whether evolution occurred after an interval of normal hematopoiesis. Screening patients for loss of phospatidyl-inositol–linked membrane proteins by FACS analysis may offer a more sensitive tool to examine the relationship between aplastic anemia and PNH.[24] No patient with PNH has subsequently had thrombotic or infectious complications, and one carried a normal pregnancy to term, raising the possibility that PNH that develops in this setting has a relatively benign course.

The relapse rate of our patients was very high, reaching an actuarial risk of 36% at 2 years. Other groups have reported similarly high relapse rates in patients treated with immunosuppression,[16,25] but not at such an early timepoint. Possibly, individuals with more active immune-mediated suppression of hematopoiesis would not have achieved remission with less aggressive regimens and remain at higher risk of relapse. Most patients who relapsed responded to an additional course of immunosuppression, suggesting that response to this modality at any time is sufficient to differentiate patients with a favorable prognosis. Although there was no significant difference in survival between patients who relapsed and patients in a sustained remission, the low number of deaths in these two groups makes our study insensitive to modest differences in outcome. The European Bone Marrow Transplantation Group SAA Working Party has reported a decrease in actuarial 10-year survival from 79.8% for patients with a sustained response to 67.1% for patients who responded and subsequently relapsed.[25]

We were unable to confirm that an ANC less than 200/mm^3 or age at diagnosis of less than 20 years carried a poor prognosis. Early deaths were higher among patients with very severe disease, but this difference did not reach statistical significance. Although 3- and 6-month response rates were also lower in patients with low ANCs, these difference also did not reach significance, and by 12 months, response rates were equivalent. The poor prognosis associated with a very low ANC may be caused by the increased risk of early infectious mortality; better supportive care and earlier response may reduce this risk.

Patients older than 20 years of age had a lower response rate at all times than younger patients, although the difference never reached statistical significance. All of the early deaths occurred in the older group, and this may account for the response difference. Almost all of the relapses also occurred in older patients, and all but one in patients with ANCs over 200. There was a significant positive correlation between age and ANC at presentation ($P \leq .001$), so it is unlikely that these are independent associations.

Several other observations deserve comment. Most of our patients had received other therapy before referral, including substantial courses of corticosteroids as well as growth factors. Corticosteroids given at standard doses (ie, 1 mg/kg/d prednisone) have no demonstrated efficacy as single agents in the treatment of severe aplastic anemia. Their use is associated with significant short- and long-term complications, including avascular necrosis. They should not be used alone for the treatment of severe aplastic anemia or empirically to treat undiagnosed pancytopenia. The role of growth factors in the treatment of aplastic anemia is uncertain.[15] They do not appear to have significant efficacy at low or standard doses, especially when given alone. It is hard to justify their use as front-line agents, or outside of a protocol setting.

The optimal first-line therapy for patients with severe aplastic anemia depends on age, severity of disease, clinical history, and eligibility for BMT. Aggressive immunosuppression with the combination of ATG and CsA appears to be the treatment of choice for young patients and patients with very low presentation ANCs who are ineligible for BMT from a histocompatible sibling donor. The high early response rate to the combination regimen also makes it an attractive treatment for other patients with severe disease. Long-term survival is comparable, although not better, than other current ATG/ALG based protocols or BMT.[6,7,26] Late malignancies have occurred in patients treated with ATG or ALG alone[27]; it remains to be determined whether CsA increases this risk and, if it does, if the increased risk is justified by the improved short-term outcome. Several other issues also remain to be addressed, including establishing the optimal duration of CsA therapy, whether CsA should be tapered or abruptly discontinued, and whether longer therapy or the addition of other agents such as growth factors will result in a higher response rate, fewer relapses, and improved long-term survival. The questions of which patients benefit from initial BMT, which patients should receive ATG with CsA reserved for treatment failure, and which patients benefit from initial aggressive immunosuppression will require further study.

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