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Retreatment with rabbit anti-thymocyte globulin and ciclosporin for patients with relapsed or refractory severe aplastic anaemia

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Summary

The management of patients with severe aplastic anaemia (SAA) who do not have a matched sibling donor and fail a course of horse anti-thymocyte globulin (h-ATG)/ciclosporin (CsA) is uncertain. Repeated courses of ATG-based immunosuppression are often employed; in children and increasingly in adults, alternative donor haematopoietic stem cell transplantation is an option. We analysed the success rate of retreatment with rabbit ATG (r-ATG)/CsA in 43 patients treated at our institution in the last 5 years; 22 were refractory (20 adults; two children) to h-ATG/CsA-based regimens and 21 (17 adults; four children) had relapsed after h-ATG/CsA-based regimens. The overall response rate was 30% in patients who were refractory to h-ATG and 65% in patients who had relapsed following h-ATG. The 1000-d survival in patients who responded to r-ATG was 90% compared with 65% in non-responders. Six patients developed a clonal haematological disorder; two were responders, two were non-responders and in two the evolution occurred before the response could be assessed at 3 months following r-ATG. Thirteen patients died; three were responders, six were non-responders and four patients died prior to 3 months when response was assessed. In our study, the response rate in refractory patients was inferior to what has been previously reported.

Keywords: aplastic anaemia, anti-thymocyte globulin, ciclosporin, refractory, relapse.

Due to age or the absence of a histocompatible donor, the majority of patients with SAA do not undergo haematopoietic stem cell transplant (HSCT) from a matched sibling and are treated instead by immunosuppression, usually the combination of a horse anti-thymocyte globulin (h-ATG) and ciclosporin (CsA) (Frickhofen & Rosenfeld, 2000). A favourable haematological response to h-ATG and CsA is observed in approximately two-thirds of patients; and the one-third who do not respond are considered refractory. Relapse among responders occurs frequently, estimated at about 35% at 5 years in one large study, with relapse defined as the requirement for further immunosuppressive drug treatment (Rosenfeld *et al*, 2003).When a more liberal definition was used, based on resumption of transfusions after achieving transfusion independence, relapse was observed in 12% of cases at 3 years (Bacigalupo *et al*, 2000). Both refractory aplastic anaemia and relapse are frequently treated with further courses of ATG. In patients who lack a histocompatible sibling, alternative donor HSCT is usually sought, with a higher success rate reported in younger patients (Georges & Storb, 2002; Bacigalupo *et al*, 2005).

The response rates of retreatment with h-ATG or rabbit ATG (r-ATG) in refractory patients or relapsed patients have varied significantly, from 22% to 77% (Marsh *et al*, 1987; Means *et al*, 1988; Stein *et al*, 1994; Tichelli *et al*, 1998; Di Bona *et al*, 1999). In three studies of patients refractory to a course of anti-lymphocyte globulin alone, retreatment resulted in a response in four of 18 (22%), three of eight (38%) and 16 of 25 (64%) cases (Marsh *et al*, 1987; Means *et al*, 1988; Tichelli *et al*, 1998). Retreatment with rabbit anti-lymphocyte globulin following horse anti-lymphocyte globulin failure resulted in response of two of eight (25%) cases (Stein *et al*,

1994). There are fewer studies assessing the success of retreatment with r-ATG in patients who fail to respond to the combination of h-ATG and CsA. In one report, 30 patients unresponsive to h-ATG were retreated with r-ATG; response was reported in 23 (77%) (Di Bona *et al*, 1999). The response rate with retreatment in relapsed patients following h-ATG have been more consistent, with results in the 50–60% range (Schrezenmeier *et al*, 1993; Tichelli *et al*, 1998).

Rabbit anti-thymocyte globulin has been used in conditioning regimens for solid organ and haematopoietic stem cell transplant and as a primary treatment in aplastic anaemia, mainly in Europe. Due to the few studies using r-ATG following failure to respond to h-ATG/CsA and the large variability of response with retreatment in this setting, we conducted a retrospective analysis at our institution of patients who received r-ATG after failing h-ATG/CsA. We also analysed the success of r-ATG in patients who relapsed after h-ATG/CsA. Here, we summarise the results of r-ATG retreatment in patients with SAA who were refractory to or who had relapsed following treatment with h-ATG.

Patients and methods

Patients

In this retrospective analysis, patients with refractory or relapsed SAA were treated with r-ATG/CsA from January 2000 to May 2005 at the Warren Grant Magnuson Clinical Center and the Mark O. Hatfield Clinical Research Center at the National Institutes of Health in Bethesda, MD, USA. All patients were enrolled on Institutional Review Board-approved clinical research protocols at the National, Heart, Lung and Blood Institute; informed consent was provided by all patients. Patients with congenital aplastic anaemia were not included. Four patients had posthepatitis aplasia and the remainder had idiopathic acquired SAA. The aim of the study was to confirm reports from other institutions of the efficacy of retreatment with r-ATG in patients who are unresponsive or relapse following h-ATG-based regimens.

Treatment regimen

After premedication with diphenhydramine and acetaminophen, r-ATG (Thymoglobulin ®; Genzyme, Cambridge, MA, USA) was administered at 3·5 mg/kg/d for five consecutive days. Patients were hospitalised for the administration of ATG and discharged when clinically stable, usually at about 2 weeks. Serum sickness prophylaxis with oral prednisone at 1 mg/kg/d was begun prior to the first dose of r-ATG, continued for 10 d and then tapered in the following week. CsA was started on day 1 at 10 mg/kg/d by mouth in divided doses q12 h. Dosing was adjusted to maintain a drug level of 200–400 ng/ml and was administered for at least 6 months. Aerosolised pentamidine was used as prophylaxis for *Pneumocystis carinii* at a dose of 300 mg every 4 weeks and for children <5 years old the dose was 120 mg every 4 weeks beginning the first week of initiating CsA therapy and continued for the 6 months of CsA administration.

Response, relapse, survival and evolution

Severe aplastic anaemia was defined as satisfying two of the three following peripheral blood count criteria: (i) absolute neutrophil count (ANC) $< 0{\cdot}5 \times 10^9$/l; (ii) absolute reticulocyte count $< 60 \times 10^9$/l; or (iii) platelet count $< 20 \times 10^9$/l (Camitta *et al*, 1976; Rosenfeld *et al*, 1995). Response was defined as no longer satisfying criteria for SAA, which almost always equated to transfusion-independence (Rosenfeld *et al*, 1995). A complete response (CR) was defined as satisfaction of all three peripheral blood count criteria: (i) ANC $\geq 1{\cdot}0 \times 10^9$/l; (ii) Hb ≥ 10 g/dl; (iii) platelet count $\geq 100 \times 10^9$/l. A partial response (PR) was defined as blood counts no longer satisfying criteria for SAA but insufficient for a CR. Evaluation of response was performed at 3 and 6 months following ATG. Refractory SAA was defined as blood counts satisfying the criteria for SAA 6 months following h-ATG.

Relapse was defined as the need for the reinstitution of immunosuppressive therapy following an initial response to h-ATG × 4 d + CsA for 6 months (Rosenfeld *et al*, 2003). Relapse occurred after discontinuation of CsA in all cases. Evolution to myelodysplasia was defined as the appearance of a new clonal disorder on cytogenetics or characteristic morphological changes on bone marrow.

Statistical methods

Kaplan–Meier analyses were used to estimate survival; 1000-d survival is shown. Overall survival was determined from the time of entry on study. Patients who underwent HSCT following r-ATG were censored at the time of transplant. Patients who were lost to follow up were censored at the time of last visit. The differences between survival curves were tested for statistical significance ($P < 0{\cdot}05$) using the chi-square test.

Results

Forty-three patients received a 5-d infusion of r-ATG followed by 6 months of orally administered CsA; 22 were refractory to h-ATG and 21 had relapsed after a response to h-ATG/CsA. Three patients were lost to follow up; one in the weeks following r-ATG, one at 12 months, and the other 18 months after r-ATG treatment. The patient who was lost to follow up prior to the 3-month visit was not included in the analysis since response could not be assessed. One patient had r-ATG infusion discontinued after 1 d due to very poor tolerability and completed the treatment course with h-ATG; this patient also was not included in the analysis. The median age for all patients was 32 years (range 8–75 years); clinical characteristics are shown in Tables I and II.

Table I. Characteristics and response in patients refractory to h-ATG.

ID	Age (years)	Sex	Prior Tx	h-ATG to r-ATG (d)	ANC	Response at 3 months	Response at 6 months	Evolution	HSCT
1*	22	F	h-ATG/CsA	194	SAA	PR	PR		
2	28	F	h-ATG/CsA	301	SAA	NR	NR		
3	66	F	h-ATG/CsA	2024	SAA	Leukaemia	NE	Leukaemia	
4	37	M	Cy/CsA	837	SAA	NR	NR		
5	32	M	h-ATG/CsA × 2; Cy/CsA	1471	SAA	PR	PR		
6*	19	M	h-ATG/CsA/MMF	198	SAA	NR	NR		
7	17	M	h-ATG/CsA/MMF	133	VSAA	NR	NR		
8	53	F	h-ATG/CsA/MMF	207	SAA	PR	PR	Leukaemia	
9	36	M	h-ATG/CsA/MMF	222	SAA	NR	NR	Trisomy 6	
10	22	M	h-ATG/CsA/MMF	159	SAA	PR	PR		
11*	26	M	h-ATG/CsA/MMF	107	VSAA	NR	NR		Haplo
12	8	M	h-ATG/CsA/MMF	263	SAA	NR	NR		
13*	19	M	h-ATG/CsA/MMF	295	SAA	NR	NR	Monosomy 7	Haplo
14	69	F	h-ATG/CsA/MMF	204	VSAA	NR	Expired		
15	66	F	h-ATG/CsA	191	SAA	Expired	NE		
16	42	F	h-ATG/CsA/MMF	167	VSAA	NR	Expired		
17	69	M	h-ATG/CsA/MMF	141	SAA	NR	NR		
18	30	M	h-ATG/CsA/MMF	205	SAA	NR	NR		
19	22	F	h-ATG/CsA/MMF	265	SAA	PR	PR		
20	69	M	h-ATG/CsA/MMF	302	SAA	NR	NR		
21	28	M	h-ATG/CsA/MMF	57	VSAA	Expired	NE		
22	32	M	h-ATG/CsA/Rapa	75	VSAA	NR	NR		Unrelated

ATG, anti-thymocyte globulin; h-ATG/CsA, horse ATG + ciclosporin; h-ATG/CsA/MMF, horse ATG + ciclosporin + mycophenolate mofetil; h-ATG/CsA/Rapa, horse ATG + ciclosporin + sirolimus; Cy/CsA, cyclophosphamide + CsA; NE, not evaluable; PR, partial response; NR, no response; SAA, severe aplastic anaemia ANC ≥ 0·2 × 10^9/l; VSAA, very severe aplastic anaemia ANC < 0·2 × 10^9/l; HSCT, haematopoietic stem cell transplantation; haplo, haploidentical; ANC, absolute neutrophil count.
*Patients with posthepatitis aplastic anaemia.

Refractory patients

The median interval (range) between first course of h-ATG and r-ATG was 205 (57–2024) d; the median age was 31 (8–66) years and the baseline median ANC was 0·205 (0·010–2·698) × 10^9/l (Table I). Five patients received r-ATG within the 6-month period following h-ATG due to worsening blood counts and deterioration of clinical status. Of the 19 patients who were evaluable at 3 months, the response rate was 26% (5/19); and of the 15 patients evaluable at 6 months, response was observed in 33% (5/15) (Table I). One patient improved between 6 and 12 months. The overall response rate among all the refractory patients was 27% (6/22). Among the non-responders, three underwent alternative donor HSCT (two patients died); one died after evolution to leukaemia; six patients died from complications of severe pancytopenia; and the remainder received other experimental therapies and/or supportive care. The median time to death was 230 (5–1082) d from receiving r-ATG.

Relapsed patients

The median time between the first h-ATG and r-ATG/CsA was 770 (414–3968) d; the median time from relapse to treatment with r-ATG was 83 (1–3696) d; the median age was 42 (8–75) years; and the median baseline ANC was 0·555 (63–2518) × 10^9/l (Table II). Of the 20 patients who were evaluable at 3 months, the response rate was 55% (11/20); and of the 19 patients evaluable at 6 months, response was observed in 68% (13/19) (Table II). One patient had a response between 6 and 12 months. The overall response rate among all the relapsed patients was 66% (14/21). The median age among responders was 52 and among non-responders was 28; the median time from relapse to r-ATG among responders was 55 and 237 d among non-responders. Three patients died from complications of pancytopenia and one patient died following alternative donor HSCT. The median time to death after r-ATG was 292 (88–388) d.

Survival and evolution

Median follow up was 380 d. The 1000-d survival for patients with relapsed SAA was 83% compared with 70% for patients with refractory disease (Fig 1A and B) and the 1000-d survival among patients who responded to r-ATG was 90% compared with 65% among non-responders (Fig 1C). The median survival was not reached in either group. Of the whole cohort, 13 patients died. Six patients underwent alternative donor

Table II. Characteristics and response in patients who relapsed after responding to h-ATG.

ID	Age (years)	Sex	Prior Tx	Relapse to r-ATG (d)	ANC	Response at 3 months	Response at 6 months	Evolution	HSCT
23	51	M	h-ATG/CsA	36	SAA	PR	PR		
24	8	F	h-ATG/CsA	437	SAA	PR	PR	Monosomy 7	Unrelated
25	52	M	h-ATG/CsA/MMF	56	SAA	NR	NR		
26	28	M	h-ATG/CsA	2368	SAA	PR	Expired		
27	13	F	h-ATG/CsA × 2	349	SAA	NR	NR		Unrelated
28	67	F	h-ATG/CsA	3696	SAA	Expired	NE	Trisomy 8	
29	29	F	h-ATG/CsA	1774	VSAA	NR	NR		
30	32	F	Cy/CsA; h-ATG/CsA	14	VSAA	NR	PR		
31	15	M	h-ATG/CsA/MMF	32	SAA	PR	PR		Unrelated
32	63	M	h-ATG/CsA	2131	VSAA	NR	PR		
33	27	F	Cy/CsA; MMF	1	SAA	NR	NR		
34	53	F	h-ATG/CsA/MMF	29	SAA	PR	PR		
35	21	M	h-ATG/CsA/MMF	132	VSAA	PR	PR		
36	18	F	h-ATG/CsA/MMF	10	SAA	PR	PR		
37	75	M	h-ATG/CsA/MMF	19	SAA	PR	PR		
38	15	M	h-ATG/CsA	125	VSAA	NR	NR		
39	57	F	h-ATG/CsA/MMF	83	SAA	PR	PR		
40	53	M	h-ATG/CsA/MMF	632	VSAA	PR	PR		
41	75	M	h-ATG/CsA/MMF	60	SAA	PR	PR		
42	42	M	h-ATG/CsA/MMF	363	SAA	NR	NR		
43	61	M	h-ATG/CsA	51	SAA	NR	PR		

h-ATG/CsA, horse ATG + ciclosporin; h-ATG/CsA/MMF, horse ATG + ciclosporin + mycophenolate mofetil; Cy/CsA, cyclophosphamide + CsA; NE, not evaluable; PR, partial response; NR, no response; SAA, severe aplastic anaemia ANC $\geq 0{\cdot}2 \times 10^9$/l; VSAA, very severe aplastic anaemia ANC $< 0{\cdot}2 \times 10^9$/l; HSCT, haematopoietic stem cell transplantation; ANC, absolute neutrophil count.

HSCT; four were non-responders, two were responders to r-ATG; three patients died and three are alive. Clonal haematological evolution occurred in six patients: four to myelodysplasia and two to leukaemia (Tables I and II).

Discussion

Although immunosuppressive therapy has decreased the morbidity and improved the survival of patients with SAA, unresponsiveness to h-ATG + CsA and relapse after successful treatment remain important problems. Proposals have been made to standardise response criteria (Camitta, 2000), but we prefer the simple definition of no longer meeting response parameters, which we and others have validated as strongly correlating to freedom from requirement for transfusions and susceptibility to infection, as well as long term (Kim *et al*, 2003; Rosenfeld *et al*, 2003). The outcome of patients who are unresponsive to immunosuppression is poor, with death from complications of pancytopenia common (Rosenfeld *et al*, 2003). The management of such cases is uncertain. Alternative donor HSCT has resulted in a survival rate of about 70% in patients of younger age (Deeg *et al*, 2001; Vassiliou *et al*, 2001); however, most studies have been small, follow up has been relatively short, and the optimal conditioning regimen has not been defined. In a recent report from the European Group for Blood and Marrow Transplantation on SAA Working Party, 38 patients with refractory SAA underwent an unrelated donor HSCT following a radiation-free conditioning; engraftment and survival was superior in younger patients (<14 years of age) when compared with older patients (Bacigalupo *et al*, 2005). Overall, outcomes in adults following alternative donor HSCT have not been as favourable, and instead of transplant, repeat courses of immunosuppression are often administered.

In an Italian multicentre study, 30 aplastic anaemia patients who had failed h-ATG + CsA received second-line treatment with r-ATG and CsA (Di Bona *et al*, 1999). r-ATG was given at 3·5 mg/kg, i.v. over 6–8 h from days 1 to 5; ciclosporin 5 mg/kg p.o., from days 1 to 180; 24 patients received granulocyte colony-stimulating factor at 5 μg/kg, s.c. from days 1 to 90. The median interval between the first and second courses of ATG was 151 d. Overall response, defined as transfusion-independence, was achieved in 23 of 30 (77%) patients after a median of 95 d and overall survival was 93% with a median follow up of 914 d, with no patient having relapsed at the time of publication. In a much smaller American experience, r-ATG ± ciclosporin was administered in combination with prednisone ± androgens in eight patients who had previously received h-ATG; two (25%) responded (Stein *et al*, 1994). In our experience, response to a course of r-ATG in patients with refractory SAA was about 30%, considerably lower than in the Italian study. There are several possible explanations for this

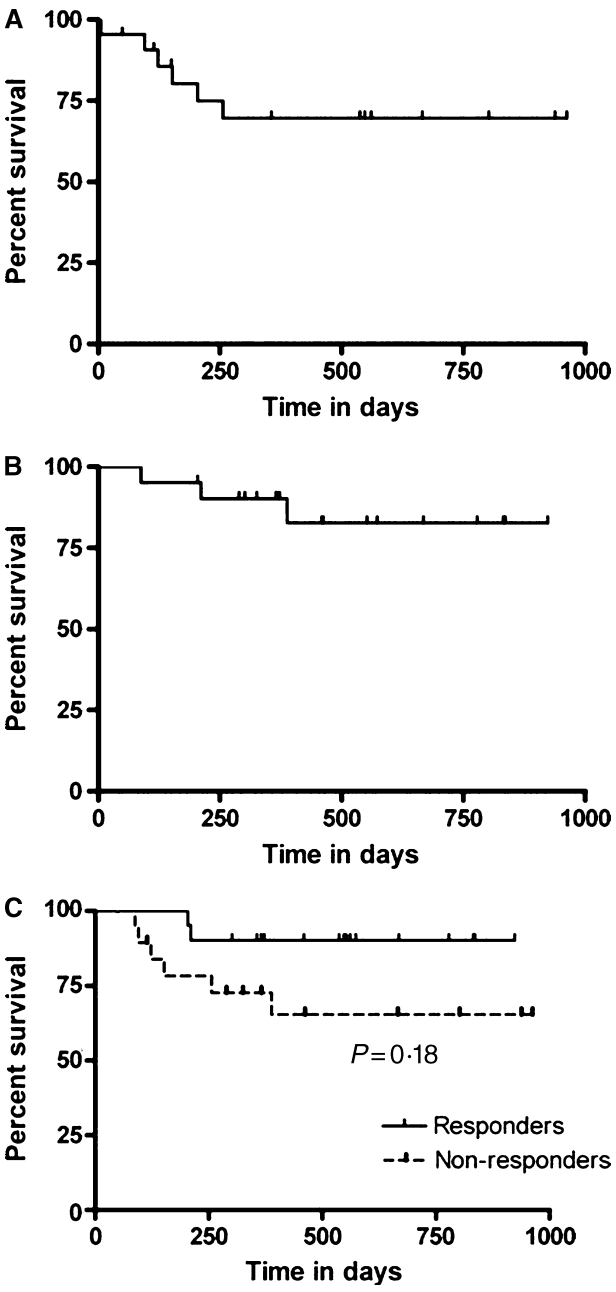

Fig 1. (A) Survival following rabbit anti-thymocyte globulin (r-ATG) in patients unresponsive to horse ATG (h-ATG)/ciclosporin (CsA); 1000-d survival was 70%. (B) Survival following r-ATG in patients who relapsed following a response to h-ATG/CsA; 1000-d survival was 83%. (C) Survival according to the response to retreatment with r-ATG; the 1000-d survival was 90% among responders and 65% among non-responders. Patients who underwent haematopoietic stem cell transplantation were censored at the time of transplantation. The difference in survival among patients who received r-ATG for refractoriness or relapse following h-ATG (A, B) was not statistically significant.

difference. First, the median time from last course of immunosuppression to r-ATG was about 2 months longer in our study compared with that reported by Di Bona *et al* (1999) (205 d vs. 151 d respectively). Since responses to h-ATG can occur up to 6 months after treatment, it is possible that some patients who responded to r-ATG in the Italian study were actually late responders to h-ATG. Secondly, the definition of response was based on transfusion-independence, whereas we defined response by peripheral blood count criteria. Although cessation of transfusion requirements almost always correlates to haematopoietic recovery, it still remains a subjective criterion that can be influenced by the physician's tolerance and the patient's adaptability to chronically low blood counts.

The median survival in refractory patients to two courses of immunosuppression in our cohort was not reached; nevertheless, the impact on quality of life with supportive care can be considerable. Therefore, the probability of survival must be weighed against the burden of supportive care on an individual basis as other treatment options are considered, such as alternative donor HSCT.

The response rate of retreatment with r-ATG in patients who relapsed following h-ATG/CsA is comparable with those reported by others, in the range of 50–60%. The occurrence of relapse or lack of response to retreatment following relapse has been associated with a worse survival compared with patients who either did not relapse or who did respond to retreatment (Schrezenmeier *et al*, 1993). Our experience has been that relapse following h-ATG/CsA does not equate to a worse survival, compared with those who do not relapse (Rosenfeld *et al*, 2003). However, here the survival at 1000 d was inferior among non-responders to retreatment with r-ATG compared with responders, but this difference in our study did not reach statistical significance. The difference in response and survival between patients who were refractory and those who had relapsed following h-ATG could reflect different pathogenesis between the two groups. A prior response to h-ATG implies an immunological pathophysiology for marrow failure and responsiveness to repeated treatment may be expected. In contrast, refractoriness to h-ATG may be due to inadequacy of the initial immunosuppressive treatment regimen (r-ATG may be more potent or provide different specificities of antibodies); severe stem cell depletion (from an immunological cause) precluding haematopoietic recovery; or a non-immune basis for disease.

Systematic studies comparing the efficacy of h- and r-ATG in SAA are lacking. In solid organ transplantation, r-ATG has been shown to be superior to h-ATG in preventing graft rejection in randomised studies (Gaber *et al*, 1998; Brennan *et al*, 1999). In aplastic anaemia, the use of r-ATG in a heterogeneous population could account for the variability of the response rates observed after a repeat course of immunosuppression. We are currently conducting a prospective study of r-ATG in patients who failed h-ATG to better define the response rate of r-ATG in the salvage setting; and a randomised prospective study, to be initiated this year at our institution, will determine the response rate of r-ATG as initial treatment as well as compare the efficacy between h- and r-ATG in treatment naïve patients.

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