

**ABO Blood Group System and
Bone Marrow Transplantation**

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The role of the ABO blood group system in determining the outcome of bone marrow transplantation was investigated in 53 patients with aplastic anemia and acute leukemia grafted from HLA-identical siblings. There was no correlation between ABO compatibility and marrow engraftment, graft rejection, or graft-versus-host disease. In 5 recipients with antibodies prior to transplantation to antigens of the

ABH system present on the cells of their donors, plasma exchange and antibody absorption in vivo were effective in permitting engraftment of ABO-incompatible bone marrow. These findings indicate that the ABO system is not a clinically significant barrier to successful bone marrow transplantation in otherwise histocompatible individuals.

BONE MARROW TRANSPLANTATION is increasing in use in the treatment of patients with aplastic anemia, acute leukemia, and immunodeficiency disease.¹⁻³ Marrow donors are usually selected from among HLA-identical siblings. Because inheritance of the ABO blood group antigens is independent of the HLA gene complex, transplants between ABO non-identical siblings are frequently considered. To define the role of the ABO system as a potential target antigen of graft rejection and graft-versus-host disease, we have analyzed data from 53 patients with transplants from their HLA-identical siblings. We have also investigated the effectiveness of plasma exchange and antibody absorption in vivo in preparing recipients for ABO-incompatible marrow transplants.

MATERIALS AND METHODS*Patients*

The study cohort was comprised of 53 patients—19 with aplastic anemia and 34 with acute leukemia. Detailed clinical information has been published.^{2,4,5} All donor-recipient pairs were

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HLA-A and -B identical. Fifty pairs were HLA-D compatible. Aplastic patients were conditioned for transplantation with cyclophosphamide ($n = 11$), total body irradiation ($n = 1$), or cyclophosphamide and total body irradiation ($n = 7$). Patients with leukemia received cyclophosphamide and total body irradiation ($n = 7$) or multiagent sequential conditioning comprised of cytosine arabinoside, 6-thioguanine, daunorubicin, cyclophosphamide, and total body irradiation ($n = 27$).^{4,5} After transplantation, patients received methotrexate to modify graft-versus-host disease.¹

Engraftment was documented by rising white cell count, platelet count, red cell count, bone marrow morphology, and peripheral blood and bone marrow karyotype and gene marker studies.⁶ Patients surviving 7 days or more were evaluated for engraftment. Graft rejection was documented using hematologic, genetic, and immunologic criteria. Engrafted patients dying before day 30 were not considered "at risk" for graft rejection. The diagnosis and staging of graft-versus-host disease was based upon previously published clinical and histopathologic criteria.¹ Engrafted patients surviving 30 days or more were considered "at risk," including two who subsequently rejected their grafts. Graft-versus-host disease was treated with high-dose corticosteroids in five patients and with antithymocyte globulin (ATG) in one patient. Patients have been identified by a three-digit numerical coding system to maintain confidentiality. Appropriate informed consent was obtained from all patients.

Gene Markers

Red blood cells obtained from peripheral blood and bone marrow samples were analyzed for ABO, Lewis, Rh, MNSs, Fy, Lutheran, Kell, Kidd, and P antigen systems^{7,8} and for red cell isoenzymes, including adenylate kinase (AK), phosphoglucomutase I (PGM₁), red cell acid phosphatase, glutamate pyruvate transaminase (GPT), and esterase D, using electrophoretic techniques.^{6,7,9}

ABO Antibody Titers

Red cell typing, cross-matching, and IgM anti-A and anti-B titers were performed as previously described.⁸ IgG anti-A and anti-B titers were determined as an indirect Coombs' test after serum absorption with Neutr-AB-Reagent (Dade Corporation, Miami, Fla.). All serum samples were tested when obtained and aliquots were frozen for sequential testing under standardized conditions.

Plasma Exchange and Antibody Absorption In Vivo

Five recipients (012, 021, 029, 039, 064) were incompatible in cross match against donor red cells before transplantation. Elution studies indicated specificity for ABO antigens exclusively. Three patients were O with A donors, one was O with a B donor, and one was A with a B donor.

To facilitate incompatible marrow infusion, plasma exchange was performed via a surgically placed external arteriovenous fistula using a modification of the NCI-I.B.M. blood cell separator¹⁰ (Celltrifuge, American Instrument Company, Silver Springs, Md.); 15–20 liters of plasma were removed and isovolumetrically replaced with donor- or AB-type fresh frozen plasma at a rate of 35–70 ml/min. ABO antibody titers, electrolytes, albumin, calcium, and magnesium were monitored serially. Calcium gluconate or magnesium sulfate were given when indicated.

On completion of the plasma exchange, recipients were transfused with 1–4 units of donor-type packed and washed red cells. Tests for bilirubin, serum hemoglobin, haptoglobin, and a direct and indirect Coombs' test were performed after each unit. Not infrequently, these units were cross-match incompatible with recipient serum but caused no adverse clinical reaction or biochemical evidence of hemolysis. One recipient received 10 units of A substance (Armour Pharmaceuticals, Phoenix, Ariz.) intravenously immediately following the plasma exchange. In all instances, donor marrow was infused within 12 hr of completion of the plasma exchange. Post-transplant, recipients generally were transfused with red cells, platelets, and granulocytes of donor ABO type.

Statistical Analysis

Patient cohorts designated by ABO identity or compatibility were compared for differences in the incidence of either graft rejection or graft-versus-host disease using Fisher's exact χ^2

Table 1. ABO Matching and Graft Rejection in Aplastic Anemia

ABO	No.	Engraftment	Rejection
O → O	5	5	1
A → A	5	4	1
B → B	2	2	1
O → A	4	4	0
O → B	1	1	1
Total	17	16	4
A → O	1	1	0
B → O	1	1	0
Total	2	2	0

test. For this analysis patients with grades 0 and I graft-versus-host disease were compared with those with grades \geq II.

RESULTS

Engraftment and Graft Rejection

Engraftment was documented in 49 of 50 evaluable patients. The single patient failing to engraft was a patient with aplastic anemia who received 10 granulocyte transfusions from his HLA-identical marrow donor in the 2 wk preceding transplantation. The ABO matching in this case was A → A (Table 1). Of the 41 engrafted patients at risk, 4 subsequently rejected their grafts. All 4 had aplastic anemia and had been conditioned with cyclophosphamide. The overall rejection rate in patients so conditioned was 29% of those at risk. The 4 episodes occurred in recipients not at increased risk of graft rejection (1, O → O; 1, A → A; 1, B → B; 1, O → B), whereas no rejections occurred in the 2 aplastic recipients at potentially increased risk ($\chi^2 = 0.76$, $p = 1.00$). The differences were not statistically significant. None of the leukemia patients rejected their grafts, including 3 additional patients at risk to reject based on ABO incompatibility (2, A → O; 1, B → A).

Graft-Versus-Host Disease

The incidence and grading of graft-versus-host disease in patients with aplastic anemia and acute leukemia are indicated in Tables 2 and 3, respectively. Twelve patients with aplastic anemia were at risk to develop graft-versus-

Table 2. ABO Matching and Graft-Versus-Host Disease in Aplastic Anemia

ABO	No.†	Grade Graft-Versus-Host Disease*					
		O	I	II	III	IV	Chronic
O → O	3	2	0	0	0	0	1
A → A	4	1	0	0	2	0	1
A → O	1	1	0	0	0	0	0
Total	8	4	0	0	2	0	2
O → A	3	2	0	0	1	0	0
O → B	1	1	0	0	0	0	0
Total	4	3	0	0	1	0	0

*Clinical grades according to Thomas et al.¹

†Number of recipients at risk (surviving \geq 30 days).

Table 3. ABO Matching and Graft-Versus-Host Disease in Acute Leukemia

ABO	No.†	Grade Graft-Versus-Host Disease*				
		0	I	II	III	IV
O → O	12	6	3	1	2	0
A → A	5	2	1	1	1	0
B → B	2	1	0	0	1	0
AB → AB	1	0	0	0	1	0
A → O	2	1	1	0	0	0
Total	22	10	5	2	5	0
O → A	2	1	0	0	0	1
B → A	1	1	0	0	0	0
Total	3	2	0	0	0	1

*Clinical grades according to Thomas et al.¹

†Number of recipients at risk (surviving ≥ 30 days).

host disease. There was no significant difference in the incidence between ABO identical pairs (2/7), minor mismatches (A → O, 0/1), or major mismatches (1/4). The two cases of chronic graft-versus-host disease occurred in ABO-identical transplants.

Twenty-five patients with leukemia were at risk to develop graft-versus-host disease. Twelve cases were observed among 22 patients, either ABO identical or with minor mismatches. One of three patients at increased risk (2, O → A; 1, B → A) developed graft-versus-host disease. The differences were not statistically significant ($\chi^2 = 0.005$, $p = 0.60$). No chronic graft-versus-host disease was observed among leukemic recipients.

Plasma Exchange

The plasma exchange and transfusion of donor-type red cells was well tolerated in all five recipients. Two developed clinical evidence of hypocalcemia which responded to calcium administration. After plasma exchange, one recipient (039) had persistent antibody against ABO antigens present on his donor's cells and was incompatible on cross match with donor-type red cells. The five recipients were transfused with red cells of the same type as the donor without clinical or biochemical evidence of hemolysis. Their clinical courses are detailed below. Data is reported as of May 1, 1977.

Recipient 021

An 18-yr-old male with acute lymphoblastic leukemia was considered for marrow transplantation in 1974. An HLA and mixed lymphocyte culture (MLC) identical male sibling was selected as marrow donor. The recipient was ABO type O and the donor A. IgM anti-A titer of 1:64 and an IgG anti-A titer of 1:4 were detected, and a cross match with recipient serum and donor red cells was positive (Table 4). The recipient was conditioned for transplantation with multiagent chemoradiotherapy.

On day -1 a 20-liter plasma exchange was performed. Immediately following this, anti-A activity was undetectable. Two units of A red cells were transfused without clinical evidence of hemolysis and were followed 6 hr later by infusion of donor marrow. The patient tolerated these procedures well. The direct

Table 4. Recipient Anti-Donor ABO Titers in Recipients of ABO-nonidentical Grafts

Recipient	ABO		Antibody Class*	Anti-ABO Antibody Titer				
	Donor	Recipient		Plasma Exchange		Posttransplant day		
				Pre	Post	0-10	10-100	> 100
021	A	O	IgM	1:64	0	1:1	0	0
			IgG	1:4	0	1:2	0	0
012	A	O	IgM	1:16	0	0	0	1:4
			IgG	0	0	0	0	0
029	B	A	IgM	1:8	0	0	1:1	NT†
			IgG	1:1	0	0	1:1	NT
039	B	O	IgM	1:8	1:1	1:1	1:2	NT
			IgG	NT	NT	NT	1:2	NT
064	A	O	IgM	1:128	0	1:2	1:2	NA‡
			IgG	0	0	0	0	NA

*See Materials and Methods for details.

†NT: not tested.

‡NA: not applicable.

Coombs' test at 37°C was transiently positive during the first 14 days post-transplant and was detected on type A cells only. Weak anti-A antibody activity was observed on day 6 following transfusion of 15 units of type O platelets. Thereafter, type A platelets were used exclusively and anti-A activity has remained undemonstrable.

The patient is currently alive more than 2 yr after transplant. Red cell antigen and red cell leukocyte enzyme studies indicate hematopoietic elements of donor origin exclusively (Table 5). Recent studies demonstrate an IgM anti-B titer of 1:1. IgG anti-B is undetectable. This antibody is presumably synthesized by the graft.

Table 5. Gene Marker and Cytogenetic Studies

Marker*	Recipient 021			Recipient 029		
	Recipient	Donor	Post-transplant	Recipient	Donor	Post-transplant
Red cell antigens						
ABO	O	A ₁	A ₁ *	A ₁	B	B*
Le	a-b+x+	a-b+x+	a-b+x+	a-b-x	a+b-x+	a-b-†
Rh	Rh ₁ Rh ₂	Rh ₁ Rh ₂	Rh ₁ Rh ₂	Rh ₁ Rh ₂	Rh ₁ Rh ₂	Rh ₁ Rh ₂
MNSs	NSs	MNS	MNS*	MNSs	MNSs	MNSs
Fy	a+b+	a+b-	a+b+*	a+b-	a+b+	a+b+*
P	P ₁	P ₁	P ₁	P ₁	P ₂	P ₁ †
Red cell enzymes						
PGM ₁	2-2	2-1	2-1*	2-1	2-1	NT
GPT	NT	NT	NT	2-1	1-1	1-1*
Esterase D	1-1	1-1	1-1	2-1	1-1	1-1*
Cytogenetic analysis‡	46,XY	46,XY	46,XY	46,XX	46,XY	46,XY*

Abbreviations: PGM₁, phosphoglucomutase 1; GPT, glutamatepyruvate transaminase; NT, not tested.

*Informative marker.

†Discordant with donor phenotype (see Discussion).

‡Peripheral blood stimulated with phytohemagglutinin (PHA); bone marrow studied without PHA.

Recipient 012

A 13-yr-old female with acute myelogenous leukemia was evaluated for bone marrow transplantation in 1975. A histocompatible male sibling was selected as the donor. The recipient was ABO type O and the donor type A. A cross match with recipient serum and donor red cells was incompatible and a recipient anti-A IgM titer of 1:16 was demonstrated (Table 4). The recipient was conditioned for transplantation with total body radiation and cyclophosphamide.

On day -1 an 18-liter plasma exchange was performed, followed by 4 units of type A erythrocytes and donor marrow. There was no clinical evidence of hemolysis. Anti-A antibody was undetectable post plasma exchange. Engraftment of donor marrow was documented on day 14 by cytogenetic analysis. On day 30 a transiently positive direct Coombs' test (37°C) was observed using both gamma and "nongamma" reagents. The reason for this finding was unclear and antibody could not be eluted from the Coombs-positive red cells. The positive direct Coombs' test resolved spontaneously. On day 110 a transiently positive IgM anti-A titer of 1:4 was observed; this was retested on three occasions.

The patient had received no recent transfusions and had no evidence of hemolysis. The patient did well clinically without evidence of graft rejection or graft-versus-host disease until day 137, when a relapse of the leukemia occurred. While leukemic cells were of recipient origin (46,XX), red cell production was demonstrated to be of donor origin. The patient died on day 178 of resistant leukemia.

Recipient 028

An 18-yr-old female with AML was considered for marrow transplantation from her histocompatible but ABO-mismatched male sibling in 1975. The recipient was type A and the donor type B. A cross match between recipient serum and donor red cells was incompatible. Incompatibility was detected against B red cells only. Recipient IgM and IgG anti-B antibody titers of 1:8 and 1:1, respectively, were demonstrated. An anti-B IgM titer of 1:256 had been reported 3 mo before transplantation. The recipient was conditioned with multiagent chemotherapy and radiotherapy.

On day -1 a 20-liter plasma exchange was performed using AB plasma, followed by transfusion of 4 units of B red cells and donor marrow. There was no evidence of hemolysis. Engraftment was documented by cytogenetic analysis (46,XY) after day 14. Results of serial antibody studies are indicated in Table 4. After plasma exchange anti-B antibody was undetectable. A positive direct Coombs' test was noted on day 31 and an anti-B antibody was eluted. On day 58 circulating IgG anti-B antibody was detected. The recipient had been receiving type B platelets but occasional units of type O platelets and granulocytes had been transfused. Additionally, after day 80 low titers of IgM anti-A antibodies were detected. Hemolysis was not observed and the patient did well until day 115, when she developed fatal interstitial pneumonitis. There was no evidence of either graft rejection or graft-versus-host disease throughout her course.

Recipient 039

A 20-year-old male with idiopathic aplastic anemia was considered for marrow transplantation in 1975. A histocompatible ABO-mismatched female sibling was selected as marrow donor. The recipient was type O and the donor B. A routine cross match was incompatible and an anti-B antibody titer of 1:8 was detected (Table 4).

A 20-liter plasma exchange was performed; following this an anti-B titer of 1:1 was demonstrated. The recipient was transfused with 2 units of B red cells, followed by total body irradiation and marrow infusion. Hemolysis was not observed. A positive direct Coombs' test was detected on days 14 and 26. The indirect Coombs' test was positive with B red cells at 24° and 37°C, but subsequently became negative. After transplantation, anti-B antibody titers at 1:1 to 1:2 were detected but hemolysis was again not observed. On day 33 the patient developed ascites and liver failure and died shortly thereafter. Posttransplant cytogenetic analysis revealed only donor (46,XX) cells.

Recipient 064

This 16-yr-old male with idiopathic aplastic anemia was transplanted from his HLA-identical female sibling in 1976. The donor was ABO type A and the recipient O. Before transplantation, the recipient had an IgM anti-A titer of 1:128 with no detectable IgG anti-A (Table 4).

A 12-liter plasma exchange was performed, followed by transfusion of 3 units of type A red cells. After plasma exchange, the IgM anti-A titer was undetectable. On days 1-10 it rose to 1:1 to 1:2. The direct Coombs' test with A red cells was positive on days 1-20. The patient is alive at day 45 and has grade III graft-versus-host disease. There is no evidence of hemolysis or graft rejection at this time. The direct and indirect Coombs' tests are negative, and there is no evidence of anti-B isohemagglutinin production. Circulating anti-A is undetectable.

Gene Marker Studies

Detailed results of gene marker and cytogenetic studies in two patients are indicated in Table 5. Recipient 021 and his donor were discordant at the ABO, MNSs, Fy, and PGM, loci. All red cells were of donor phenotype 550 days posttransplant. Recipient 029 differed from her male donor for the ABO, Lewis, Fy, P, GPT, and esterase D markers. Cytogenetic analysis of peripheral blood and bone marrow posttransplant revealed male (46,XY) cells exclusively. The ABO, Fy, GPT, and esterase D loci were of donor phenotype. Results at the Lewis locus reflected the secretor status of the recipient as this antigen system is not intrinsic to the red cell. We have made similar observations in two additional patients. Discordant results at the P locus probably represented transfused red cells. As P₂ is defined by the absence of P₁, this finding would be anticipated in P₂ patients transfused with small numbers of P₁ cells.

DISCUSSION

The data presented indicate that the ABO antigens are not clinically important targets of graft rejection or graft-versus-host disease in bone marrow trans-

plantation. The incidences of successful engraftment, graft rejection, and graft-versus-host disease were unaffected by ABO compatibility.

Five recipients with antibodies against antigens of the ABH system present on the cells of their donor before transplantation were successfully engrafted following plasma exchange and antibody absorption *in vivo*. Graw and co-workers successfully engrafted one of two leukemic recipients from an ABO-nonidentical donor (A \rightarrow O).¹¹ The second patient failed to engraft despite two attempts at transplantation. Thomas and co-workers transplanted two ABO-nonidentical patients (A \rightarrow O) with acute leukemia.¹² They observed graft rejection in one, associated with a rise in anti-A titer. The second patient died on day 37 with graft-versus-host disease. An earlier report by Storb and co-workers¹³ indicated a high incidence of graft rejection among recipients of ABO-nonidentical grafts (2 of 3). This difference was not statistically significant.⁸ ABO identity has not been proven to be critical in determining graft rejection or graft-versus-host disease in a larger series.¹⁴

ABO antigens can serve as potential targets of graft rejection or graft-versus-host disease. The intensive immunosuppression given to marrow graft recipients could conceivably mask the contribution of ABO antigens to graft rejection. Nevertheless, the four rejection episodes observed were in recipients of ABO-identical grafts. Likewise, ABO identity had no significant effect on the incidence or severity of graft-versus-host disease. It is possible that methotrexate therapy modified the contribution of ABO disparity. While methotrexate has been effective in preventing or modifying graft-versus-host disease induced by minor histocompatibility loci in rodents¹⁵ and dogs,¹⁶ it has been relatively less effective in man, as indicated by the high incidence in this and other series.^{1,2,5,12}

Finally, the possibility that posttransplant immune incompetence explains the failure to find a correlation between ABO identity and graft-versus-host disease is unlikely, as we have observed normal isohemagglutinin titers to irrelevant ABO antigens after transplantation, *i.e.*, anti-B antibody in O \rightarrow A grafts. Whether the failure to detect circulating antibody to relevant ABO antigens is related to induction of specific tolerance or absorption *in vivo* is uncertain and is under investigation.

The demonstration of anti-donor ABO antibody following plasma exchange was unanticipated. This finding could be explained either by antibody diffusion from the extravascular space or by passive transfer via blood product transfusions. In recipient 012, however, neither explanation appears likely, and persisting recipient B-lymphocyte function appears to be a more tenable hypothesis. A similar observation has been made by Thomas and co-workers.¹²

The data presented here indicate that the ABO blood group system does not play a significant role as a transplantation antigen in marrow grafting. The situation in other types of organ grafts is controversial. In kidney grafting ABO incompatibility increases the frequency of acute rejection and early failure to function.¹⁷ The proportion of functioning kidneys at selected intervals post-transplant is, however, independent of ABO compatibility.¹⁸ While initial reports suggest a direct correlation between ABO compatibility and skin graft survival,^{19,20} critical analysis reveals a more complex and as yet unresolved relationship.^{21,22} Finally, ABO compatibility does not appear to be critical in effecting corneal graft survival.²³

The decision to use bone marrow transplantation in a given patient is complex, involving clinical, hematologic, and immunologic considerations. Patients selected for transplantation with otherwise histocompatible donors should not be excluded because of ABO incompatibility. Hopefully, continued investigations will suggest those antigen systems which are important in determining graft outcome and define that group of patients most likely to benefit from marrow transplantation.

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