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LONG-TERM SURVIVAL OF DLA-MATCHED SEGMENTAL SMALL-BOWEL ALLOGRAFTS IN DOGS[1]

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The aim of this study was to investigate the combined effect of DLA matching and immunosuppressive therapy on the survival of segmental small-bowel allografts in dogs. Orthotopic segmental small-bowel transplantations (25 to 30% of total small bowel length) were performed in two stages: first a heterotopic segmental small bowel transplantation, followed after 5 to 8 weeks by a second-stage operation during which the heterotopic graft was placed in an orthotopic position and the native small bowel was resected. All dogs received cyclosporine immunosuppression. Control dogs (n=4), subjected to total enterectomy, survived 37.3±7.1 days (mean ± SEM). Recipients of DLA-mismatched small bowel grafts (n=6) survived 113.2±37.0 days, which was a significantly shorter time than dogs with a DLA-matched graft (n=6, 211.5±38.8 days, $P<0.05$). None of the matched allografts was rejected during CsA treatment, whereas four of six mismatched grafts were ($P<0.05$). The control dogs uniformly showed progressive weight loss, steatorrhea, and hypoalbuminemia. The dogs with DLA-mismatched grafts did not regain initial body weight, whereas animals with DLA-matched grafts recovered preoperative weight after 20 weeks. Both transplanted groups showed near-normal fecal fat excretions and constant serum albumin, cholesterol, and triglyceride levels, whereas serum total protein levels increased during follow-up. We conclude that segmental small bowel transplantation between DLA-matched donor-recipient pairs results in long-term survivors with an adequate nutritional status. This may have important implications for future living-related small-bowel transplantation.

Initial clinical experience with simultaneous small-bowel/liver transplantation, and the development of improved im-

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munosuppressants such as FK-506 and rapamycin, enhance the expectations that small-bowel transplantation could be used to treat the short-bowel syndrome (*1–3*). However, rejection with subsequent sepsis and development of lymphoproliferative disorders remain the major reasons for most clinical failures (*4, 5*). Moreover, in multivisceral allografting the intestinal transplant seems to be the most immunogenic component of the procedure (*6*).

Recently, in a nonimmunosuppressed heterotopic canine SB transplant model, we demonstrated that matching for canine major histocompatibility complex antigens results in prolonged survival times of intestinal grafts in proportion to the degree of histocompatibility between donor and recipient (*7*).

The present study was undertaken to investigate the combined effect of dog leukocyte antigen matching and immunosuppressive therapy on the survival of canine SB grafts. Regarding a potential role for living-related SB transplantations, in which only a partial resection of the donor SB is possible, we also studied functional aspects of segmental allografting.

MATERIALS AND METHODS

Animals and experimental groups. In total, 24 healthy adult Beagle dogs (Harlan, Zeist, the Netherlands) weighing 10–20 kg were used. We created 3 experimental groups: group 1 (n=4), short bowel controls in which a total enterectomy was performed; group 2 (n=12), fully DLA-mismatched orthotopic segmental ileal allografts; and group 3 (n=8), fully DLA-matched orthotopic segmental ileal allografts. In all dogs of the allotransplant groups transplantations were performed by exchanging an SB graft between dogs of selected donor-recipient pairs.

Animal care. The experimental protocols adhered to the rules laid down in The Dutch Animal Experimentation Act (1977) and the "Guidelines on the Protection of Experimental Animals" published by the Council of the European Committee (1986). Specific protocols were approved by the Committee on Animal Research of the Erasmus University, Rotterdam, the Netherlands. Animals were killed if their general condition deteriorated or if they lost more than 30% of their preoperative body weight.

DLA matching. Tissue typing for antigens of the canine MHC, the DLA complex, was achieved by serologic methods (class I antigens) and mixed lymphocyte cultures (class II antigens) as described previously (*8, 9*). In brief, typing for class I antigens was performed with a battery of 60–90 alloantisera using one- and two-stage microlymphocytotoxicity tests. These antisera define the antigens belonging to three closely linked series, DLA-A (alleles 1,2,3,7,9, and R20), DLA-B (alleles 4,5,6,10, and 13) and DLA-C (alleles 11 and 12). Typing for class II antigens was done with a unilateral mixed lymphocyte culture. Identity for class II antigens (DLA-D) was based on the absence of significant stimulation as compared with autologous controls. The selection of donor-recipient pairs in group 2 was based on a two-haplotype difference, and in group 3 on a two-haplotype similarity. Only nonlittermate donor-recipient pairs were selected (Table 1).

Operative technique. All dogs of the control group underwent an enterectomy from the ligament of Treitz to about 10 cm proximal to the ileocecal valve. Intestinal continuity was restored by a single-layer end-to-end anastomosis of distal duodenum and terminal ileum (Fig. 1C).

In the allotransplant groups an SB transplantation was performed in two stages. First, a heterotopic SB transplantation was carried out as described previously (*10*). Briefly, a loop of distal ileum (length 75–115 cm) was isolated on a vascular pedicle. After revascularization the graft was divided into two parts: a blind-ending loop ileostomy (length 15–25 cm) and an isoperistaltic Roux-en-Y loop (length 55–75 cm, which is 25–30% of total SB length) in continuity with the host's terminal ileum. The loops were exteriorized as cutaneous ileostomies. Continuity of the residual intestine was achieved by single-layer end-to-end anastomosis (Fig. 1A).

After 5–8 weeks, during a second stage operation the native SB from the ligament of Treitz to about 10 cm proximal to the ileocecal valve was resected, and the heterotopic Roux-en-Y loop was placed in an orthotopic position by end-to-end anastomosis with the distal duodenum (Fig. 1B).

TABLE 1. DLA typing and donor-recipient pairs of successfully transplanted dogs

Experimental group	DLA-A/B/C (class I antigens)		MLR[a]
	Recipient	Donor	
Group 2 (DLA-mismatched)	1,2/5,13/11	2,9/4,6/11,12	+
	2,3/4/11	1,9/4,13/12	+
	1,9/4,13/12	2,3/4/11	+
	7,9/4/12	1,9/6,13/12	+
	2,3/5,10/11	2,9/4,6/11,12	+
	2,9/4,6/11,12	2,3/5,10/11,12	+
Group 3 (DLA-matched)	2,7/4/11	2,7/4/11	—
	2/4/11	2/4/11	—
	2,9/4/11,12	2,9/4/11,12	—
	2,9/4/11,12	2,9/4/11,12	—
	2,7/4/11	2,7/4/11	—
	2,7/4/11	2,7/4/11	—

[a] Identity for class II antigens was based on the absence (−) of significant stimulation in mixed lymphocyte reactions as compared with autologous controls.

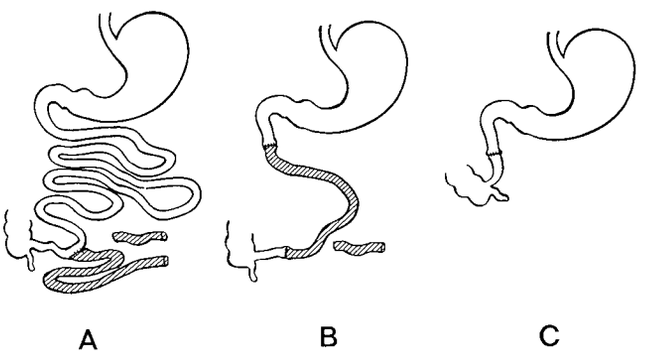

FIGURE 1. Model of canine small-bowel transplantation: (A) Heterotopic small-bowel transplantation consisting of a blind-ending loop ileostomy and an isoperistaltic Roux-en-Y loop in continuity with the host's terminal ileum; (B) orthotopic position of small-bowel graft after resection of the host's small-bowel; (C) enterectomy with end-to-end anastomosis of distal duodenum and terminal ileum.

Postoperative treatment. Cyclosporine (Sandimmune, Sandoz, Basel, Switzerland) was dissolved in olive oil. From one day before operation until the end of the first postoperative week all animals received 15 mg/kg/day CsA intramuscularly, and thereafter 30 mg/kg/day CsA orally. From postoperative day 200 onward CsA treatment was gradually tapered and stopped between days 217 and 267.

Postoperative monitoring. All animals were weighed once a week. At regular intervals blood samples were drawn in which plasma trough levels of CsA were measured using the cyclo-Trac SP radioimmunoassay kit (Incstar Corporation, Stillwater, MN). Fecal fat excretion was determined using the method of van de Kamer (*11*). Serum total protein and albumin levels were measured by means of the Biuret method and the bromcresol-green method (Boehringer, Mannheim, GmbH), respectively. Serum triglyceride levels were determined colorimetrically using the triglyceride GPO PAP system (Boehringer). The Monotest cholesterol (Boehringer) was used to measure serum cholesterol levels.

Morphology. During both operations full-thickness biopsies were taken from native and grafted SB, and at regular intervals mucosal biopsies were obtained by forceps from a cutaneous stoma. At necropsy full-thickness biopsies were taken from the SB graft as well as from the recipient's native SB, liver, lung, spleen, vascular anastomosis, mesenteric lymph nodes and skin. Biopsies were fixed in 10% buffered formalin, dehydrated, and embedded in paraffin. Hematoxylin-azophloxin–stained sections (4–5 μm) were examined by light microscopy.

Statistics. All data are expressed as means ± SEM. Survival data were analyzed using the Wilcoxon rank-sum test. Statistical comparisons between the experimental groups of weights, fecal fat contents,

and biochemical parameters were performed using one-way analysis of variance followed by the Student-Newman-Keuls test. Comparisons within a group were performed using paired Student's t tests. For all data $P<0.05$ was considered significant.

RESULTS

Postoperative course. Seven of the 24 dogs (none in group 1, six dogs in group 2, and one in group 3) died of technical failure prior to the sixth postoperative day: 5 dogs revealed a thrombus formation at either the arterial or venous anastomosis, one dog had an insufficient intestinal anastomosis, and one dog showed a large hematoma in the abdomen. At day 14 posttransplant one dog of group 3 died of a perforation in the SB graft caused by taking a mucosal biopsy with the forceps. Histologic examination showed no signs of rejection or graft-versus-host disease in the former dogs. These 8 animals were excluded from further analysis.

Survival. Survival rates of the 16 successfully operated animals and causes of death are listed in Table 2.

All four dogs of group 1, in which a near-total SB resection was performed, showed persistent diarrhea and weight loss. Eventually all these animals were killed because of progressive weight loss of more than 30% between postoperative days 28 and 58 (survival 37.3±7.1 days, mean ± SEM). At necropsy no abscesses, obstructions, or perforations were found.

The mean survival in group 2 was 113.2±37.0 days (range 28–272 days, $P<0.05$ vs. group 1). Four of the six dogs had to be killed because of a deteriorating condition marked by loss of appetite, diarrhea, and weight loss. Autopsy showed intestinal grafts with a thickened and friable SB wall. Histopathological examination showed rejection of the SB grafts with a diffuse mono- and polymorphonuclear cell infiltrate, transmural intestinal necrosis, and endovasculitis in the submucosa and muscularis propria. At posttransplant day 162 one dog had to be killed because of diffuse wart formation. Microscopic examination did not reveal signs of rejection of the SB graft. Only one dog of group 2 survived the 200-day period after which CsA therapy was tapered off. After stopping CsA therapy at day 250, the general condition deteriorated and the dog was sacrificed at day 272. Histologic examination of the SB grafts showed chronic rejection of the SB graft characterized by a diminished villus length and a mononuclear cell infiltrate in the muscularis propria. No signs of GVHD were noted.

Dogs of group 3 survived 211.5±38.8 days (range 99–361 days, $P<0.05$ vs. groups 1 and 2). During CsA treatment none of the animals suffered from rejection ($P<0.05$ vs. group 2, chi-square test). Three animals were killed at days 99, 145, and 161 because of herpes infection, perforation of the native terminal ileum, and diffuse wart formation, respectively. The SB grafts of these three dogs showed no rejection. Three dogs survived the 200-day CsA treatment period; after stopping CsA therapy at days 217, 217, and 267 these dogs showed progressive weight loss and were sacrificed at posttransplant days 248, 255, and 361, respectively. After autopsy microscopic examination showed evidence of chronic rejection in the SB transplants. No signs of GVHD were seen.

Weights. All control dogs progressively lost weight—significantly more than both transplanted groups (Fig. 2). Eventually they lost more than 30% of their preoperative weight. Dogs of groups 2 and 3 showed prolonged weight loss. Animals of group 2 did not regain their preoperative weight: 16 weeks after orthotopic placement of the graft, body weight averaged 91.0± 3.0% (mean ± SEM) of initial body weight. The surviving animals of group 3 regained their preoperative body weights only from 20 weeks posttransplant onward.

Serum parameters. During the experimental period serum albumin levels significantly decreased in group 1 ($P=0.001$ week 5 versus week 0, [Table 3]). Serum albumin levels remained constant in group 3 during the experimental period, but in group 2 eventually decreased ($P=0.019$ week 15 versus week 0).

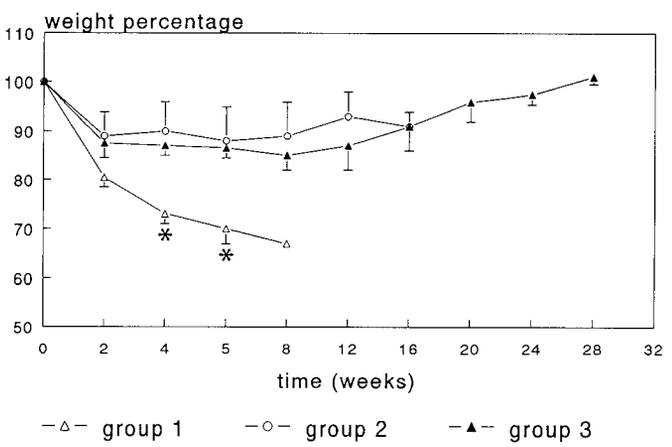

FIGURE 2. Body weight percentages after performing enterectomy or orthotopic small-bowel transplantation at 0 weeks. (*)$P<0.05$, group 1 compared with groups 2 and 3.

TABLE 2. Survival rates and causes of death

Experimental group	Survival (days)	Cause of death
1 (Short bowel)	28	Weight loss >30%
	28	Weight loss >30%
	35	Weight loss >30%
	58	Weight loss >30%
2 (DLA-mismatched)	28	Acute rejection
	56	Acute rejection
	62	Acute rejection
	99	Acute rejection
	162	Diffuse wart formation
	272	Chronic rejection
3 (DLA-matched)	99	Herpes infection
	145	Perforation bowel
	161	Wart formation
	248	Chronic rejection
	255	Chronic rejection
	361	Chronic rejection

TABLE 3. Serum total protein, albumin, cholesterol, and triglyceride levels (mean ± SEM)

Group[a]	Week	Total protein (g/L)	Albumin (g/L)	Cholesterol (mmol/L)	Triglyceride (mmol/L)
Group 1					
	0	61.10±2.46	33.25±1.11	3.26±0.30	0.31±0.06
	5	73.48±4.69	24.03±0.98[b,c]	2.86±0.78	0.38±0.05
Group 2					
	0	63.68±3.11	32.00±0.74	3.45±0.23	0.33±0.04
	5	67.30±4.10	29.05±4.05	3.28±0.47	0.47±0.22
	10	71.30±5.30	28.40±3.40	2.81±0.22	0.48±0.02
	15	81.25±8.98[b]	21.90±3.90[b]	2.34±0.29	0.73±0.24
Group 3					
	0	59.32±2.18	31.72±0.65	3.10±0.25	0.36±0.10
	5	64.13±3.16	32.43±1.12[c]	3.11±0.25	0.56±0.07
	10	64.35±1.36	31.92±0.78	3.07±0.17	0.66±0.04
	15	72.15±4.49[b]	28.50±1.57	3.36±0.21	0.61±0.04

[a] Group 1: short bowel control; group 2: DLA-mismatched; group 3: DLA-matched.

[b] $P<0.05$ versus preoperative values (week 0) in the same group.

[c] $P<0.05$ group 1 versus group 3.

At 5 weeks postoperatively serum albumin levels were significantly reduced in group 1 as compared with group 3 (P=0.001). In contrast, serum total protein levels showed increasing values in all groups during follow-up (group 2, P=0.044 week 15 versus week 0; group 3, P=0.021 week 15 versus week 0). Serum cholesterol and triglyceride levels were not different between or within the experimental groups during the experimental period.

Fecal fat excretion. At 2–5 weeks posttransplant, fecal fat excretion in the control group was significantly higher than in groups 2 and 3 (P<0.05, Fig. 3). Although both transplanted groups showed slightly increased fecal fat excretions, these differences were not statistically significant compared with preoperative values. Figure 3 also shows the elevated fecal fat excretions from three dogs of group 2 with a rejecting SB graft.

CsA levels. Plasma trough levels of CsA showed considerable variation (Fig. 4). However, in the control group CsA levels showed decreasing values (P=0.041 week 5 versus week 2). At four weeks postoperatively CsA levels of group 3 were significantly higher than CsA levels of groups 1 and 2. Thereafter groups 2 and 3 showed comparable CsA levels.

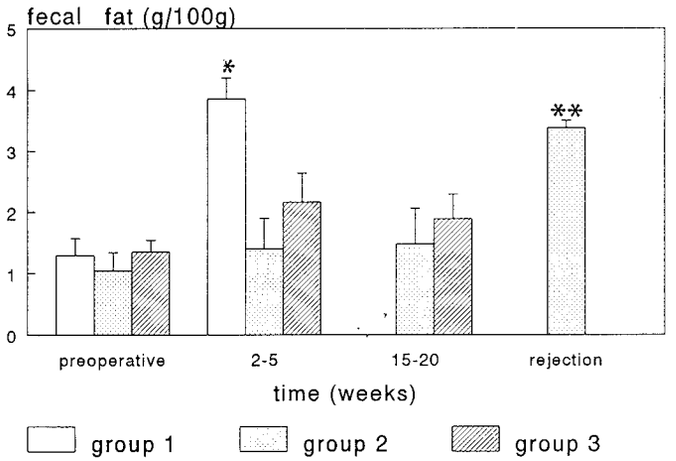

FIGURE 3. Fecal fat excretions before and after performing enterectomy or orthotopic small-bowel transplantation at 0 weeks. (*)P<0.05, group 1 compared with groups 2 and 3. (**)P<0.05, rejecting grafts of group 2 compared with nonrejecting grafts of the same group.

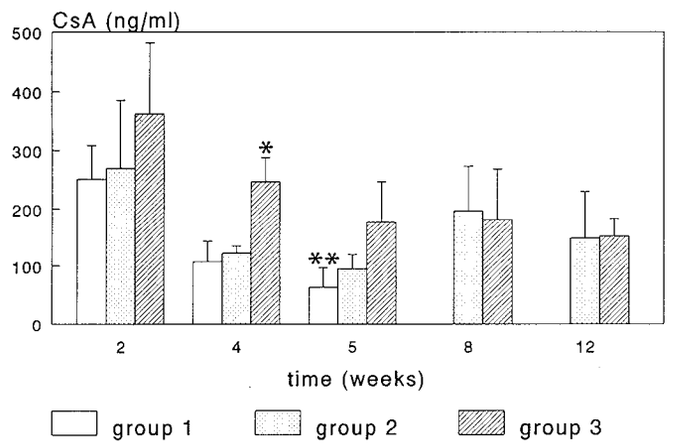

FIGURE 4. Cyclosporine levels after performing enterectomy or orthotopic small-bowel transplantation at 0 weeks. (*)P<0.05, group 3 compared with groups 1 and 2. (**)P<0.05 compared with the same group at 2 weeks after enterectomy.

DISCUSSION

Intestinal transplantation is expected to be the ultimate therapeutic treatment for adult patients with irreversible intestinal failure (*12, 13*). Indeed, recent clinical and experimental experiences with SB transplantations are promising (*1–3, 14*). However, rejection, GVHD, infectious complications, and lymphoproliferative disorders remain major problems to be solved (*4–6*).

In the present study we demonstrated that long-term survival of canine SB transplants can be achieved using fully DLA-matched donor-recipient combinations and CsA immunosuppression. Although CsA considerably prolonged graft survival, DLA matching resulted in significantly longer survival rates compared with the DLA-mismatched donor-recipient pairs. In addition, during the CsA treatment period none of the matched allografts was rejected, whereas in the mismatched group four of six dogs suffered from graft rejection. Our findings are also in accordance with the observation of Deltz et al., who reported a successful clinical case of SB transplantation using an HLA-matched donor-recipient combination (*15*).

In this study, we show that segmental transplantation of 25–30% of total SB length is able to overcome the symptoms of a surgically created lethal short bowel syndrome in dogs. The transplanted animals showed reversible weight loss, whereas all control dogs progressively lost weight. This has also been reported in rat studies using a short-bowel control group (*16, 17*). In our study, however, the surviving dogs of the matched group regained their initial body weight only 20 weeks after orthotopic positioning of the SB graft. Prolonged weight loss was not seen by Diliz-Perez et al. in their long-term surviving dogs after transplantation of the entire SB (*18*). This suggests that the segmental grafts in our study initially had a limited absorptive surface, structurally as well as functionally. An adaptation process probably took place, as documented in a pig study by Kimura et al., in which the recipients of segmental jejunal allografts regained their preoperative weight by day 50 posttransplant (*19*). The longer period of weight loss in our study may reflect the less-pronounced adaptive capacity of adult canine SB compared with the intestine of growing pigs.

Segmental SB transplantation resulted in normal serum albumin levels, as has been reported by others in rat studies (*20, 21*). However, 15 weeks after transplantation the mismatched group showed decreased albumin levels that could be attributed to chronic rejection. Unlike the transplanted groups, the controls developed hypoalbuminemia within 5 weeks, again showing intestinal failure after enterectomy. Remarkably, the transplanted groups showed increasing serum total protein levels. As serum albumin remained constant this rise of total protein is probably caused by an increase in acute phase proteins or serum globulins. This phenomenon has also been reported by Raju, who demonstrated increased serum globulin after total SB autotransplantation in dogs (*22*).

The control dogs developed steatorrhea, whereas the transplanted dogs showed near-normal fecal fat excretions. This is in parallel with the normal serum cholesterol and triglyceride levels in our transplanted animals. This means that even short segments of transplanted ileum can result in physiologic fat absorption. This is in contrast to the results of Diliz-Perez, who found increased fecal fat excretion after total SB transplantation compared with fecal fat excretion in normal control dogs (*18*). However, in the latter study the control dogs did not receive CsA, which by itself—or as a result of the oily vehicle—can induce decreased fat absorption (*23*). The dogs of the mismatched group with a rejecting graft showed steatorrhea and developed a trend toward decreased serum cholesterol levels, demonstrating the deleterious effect of rejection on the fat-absorptive capacity, and thus CsA absorption, of SB grafts.

Oral CsA is absorbed through the small bowel (*24*). To circumvent inadequate CsA levels in the early postoperative period, we treated all animals with CsA intramuscularly from one day preoperatively until the end of the first preoperative week. This regimen resulted in comparable plasma CsA levels in all three experimental groups. When oral CsA treatment was instituted, plasma levels in the short-bowel control group diminished uniformly, which emphasizes that the SB is the site of CsA absorption (*24*). At 4 weeks posttransplant reduced CsA levels were found in the mismatched group, probably caused by graft rejection in several dogs. However, in the matched group, and from 5 weeks onward in the mismatched group, the segmental SB grafts were sufficiently capable of absorbing CsA to maintain plasma CsA levels of about 200 ng/ml.

In the present study four dogs probably suffered from toxic CsA side-effects. Recent clinical SB transplantation studies report frequent bacterial, fungal, and CMV infections, and a high rate of lymphoproliferative disorders caused by vigorous immunosuppression (*4, 5*). It remains to be determined whether reducing immunosuppressive treatment will result in fewer toxic effects without inducing graft rejection or GVHD.

In conclusion, it is possible to achieve long-term survival of canine SB grafts using DLA-matched donor-recipient pairs. Additionally, segmental ileal allografts can serve as effective substitutes for resected SB and maintain an adequate nutritional status of recipient dogs. This may have important implications for clinical SB transplantation in which the use of living-related segmental SB grafts leads to better HLA matching; this could reduce the need for potential toxic immunosuppression with improved long-term results.

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