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Prolongation of Canine Renal Allograft Survival by Combining Tacrolimus With Antimetabolic Agents

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THE SYNERGISTIC combination of immunosuppressive drugs is thought to provide a better therapeutic index with fewer side effects than single-drug therapy. Tacrolimus (FK 506), an inhibitor of interleukin-2 (IL-2) synthesis, is a potent immunosuppressive agent that has various adverse effects including nephrotoxicity, neurotoxicity, diabetogenesis, and infectious complications.[1] Experimental models have shown that antimetabolic agents are good candidates for combination with tacrolimus.[2,3] Several antimetabolic agents, azathioprine (AZA), mizoribine (MIZ), mycophenolate mofetil (RS), and ethyl o-[N-(p-carboxyphenyl)-carbamoyl]-mycophenolate (CAM), were tested alone and in combination with tacrolimus to determine if they could improve canine renal allograft survival, while reducing immunosuppression-related adverse events.

MATERIALS AND METHODS

Adult mongrel dogs were used for donors and adult beagle dogs were used for recipients. Canine kidney transplantation was performed using standard operative procedures. After transplanting one kidney allograft into the right iliac fosia, bilateral native nephrectomies were performed. Experimental groups were divided into single-drug groups and combined-drug groups. The control group received no treatment. The FK 506 dose chosen (0.5 mg/kg) for this study was one third of the therapeutic dose. Single-drug doses of antimetabolites were 0.5 and 1.0 mg/kg of AZA, 2.5 and 5.0 mg/kg of MIZ, 20 and 40 mg/kg of RS, and 20 and 40 mg/kg of CAM. Combined-dose groups were FK 506 (0.5) + AZA (0.5), FK 506 (0.5) + MIZ (2.5), FK 506 (0.5) + RS (20), and FK 506 (0.5) + CAM (20). Immunosuppression was given daily for 90 days. Animals surviving 90 days were killed. Creatinine (Cr), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), and blood glucose (GLU) were monitored at least twice weekly.

RESULTS

Single treatment with all agents, except AZA, was significantly better than control (9.5 days median survival). Toxicity, particularly gastrointestinal, was seen more frequently in the higher-dose single-treatment groups than in the lower-dose single-treatment groups. Because the survival of the low and high dose-treated groups was similar, combination with tacrolimus was only carried out with the lower doses of the antimetabolic agents. Survival of animals treated with tacrolimus and antimetabolic agents was significantly better than that of single antimetabolic agents alone for all groups. Survival and renal function of the combination groups is shown in Fig 1. Only the combination of tacrolimus and MIZ was significantly better than tacrolimus treatment alone (16 days median survival). Toxic events in the combination groups were similar to the toxic events seen in their respective single-drug groups, but were less severe than the toxicity related to the higher single dose of the antimetabolic agent. Gastrointestinal toxicity, diarrhea, vomiting, and severe weight loss were the most

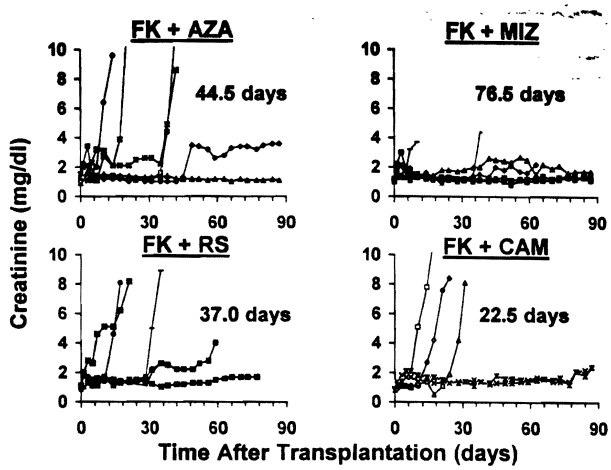

Fig 1. Renal function and median survival of combination-treated groups.

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frequent adverse events seen. The RS and CAM groups were especially troubled by gastrointestinal toxicity. Only two incidences (2.4%) of hepatic toxicity (AST or ALT > 100 U/L) were seen throughout the study. No bone marrow suppression or diabetogenicity was seen.

DISCUSSION

This study shows that the combination of tacrolimus and antimetabolic agents significantly prolongs canine renal allograft survival, without hepatotoxicity, diabetogenicity, or bone marrow suppression. The combination of tacrolimus with antimetabolites is synergistic and does not appear to increase toxicity. The effect is especially pronounced with the combination of MIZ and tacrolimus. The survival of the combined group is not only significantly better than MIZ alone, but also tacrolimus alone. MIZ is an especially interesting agent for future application to human kidney transplantation. Because MIZ is excreted through the kidney, as rejection begins to strike the allograft MIZ levels in the blood rise.

REFERENCES

1. Todo S, Ueda Y, Demetris AJ, et al: Surgery 104:239, 1988
2. Platz KP, Sollinger HW, Hullett DA, et al: Transplantation 51:27, 1991
3. Tanabe M, Todo S, Murase N, et al: Transplantation 58:23, 1994