

REVERSAL OF ACUTE REJECTION  
EPISODES BY DEOXYSPERGUALIN  
(NKT-01) IN DOGS RECEIVING  
RENAL ALLOGRAFTS

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Deoxyspergualin (NKT-01), an analogue of spergualin,<sup>1)</sup> was synthesized by IWASAWA *et al.* in 1982<sup>2)</sup> and although its immunosuppressive properties have been reported in mice and rats,<sup>3-5)</sup> immunosuppressive effects have yet to be sufficiently recognized in large experimental animals.<sup>6)</sup> Recently, AMEMIYA *et al.* reported the preventive effect of NKT-01 on the rejection of renal allografts in dogs, and suggested that

NKT-01 may be useful in clinical organ transplantation.<sup>7)</sup> In this study we have explored the efficacy of NKT-01 in treating acute rejection episodes in dogs receiving renal allografts.

Unrelated outbred beagle dogs were used for the experiment. Renal allografting was performed as previously described.<sup>8,9)</sup> Briefly, grafted kidneys were placed in the iliac fossa with end-to-end anastomosis of the renal artery to the external iliac artery and end-to-side anastomosis of the renal vein to the external iliac vein, and implantation of the ureter into the base of the urinary bladder. Plasma creatinine (p-Cr) and blood urea nitrogen (BUN) tests were performed after the operation until the animal died. NKT-01 was supplied from Takara Shuzo Co., Ltd., Kyoto.<sup>10)</sup> It was dissolved in saline and administered intravenously from the day of acute rejection onset. Details of the administered dose and schedule are shown in Fig. 2. A control group of dogs received no treatment after the operation. Onset of rejection was defined as acute rise of p-Cr. BUN levels and clinical signs such as heat up of the abdominal transplantation site and an increase in water consumption were also considered to diagnose the onset of rejection. Dead or moribund-sacrificed animals were subjected to macroscopic and microscopic examinations.

Fig. 1. Serial changes of plasma creatinine levels (p-Cr) after allogenic renal transplantation in control dogs.

\* Moribund sacrificed, \*\* died.

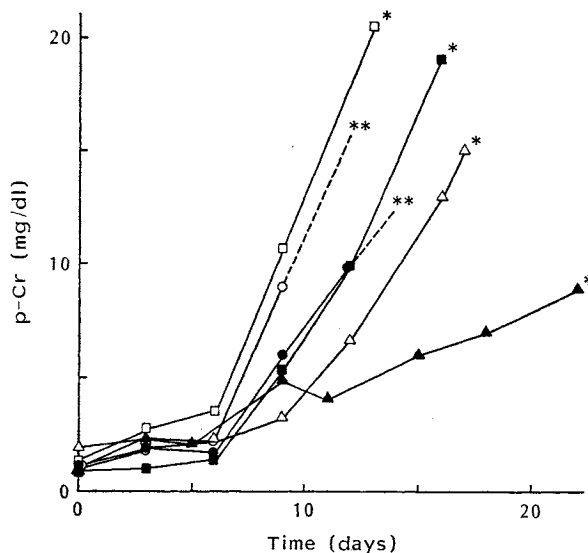
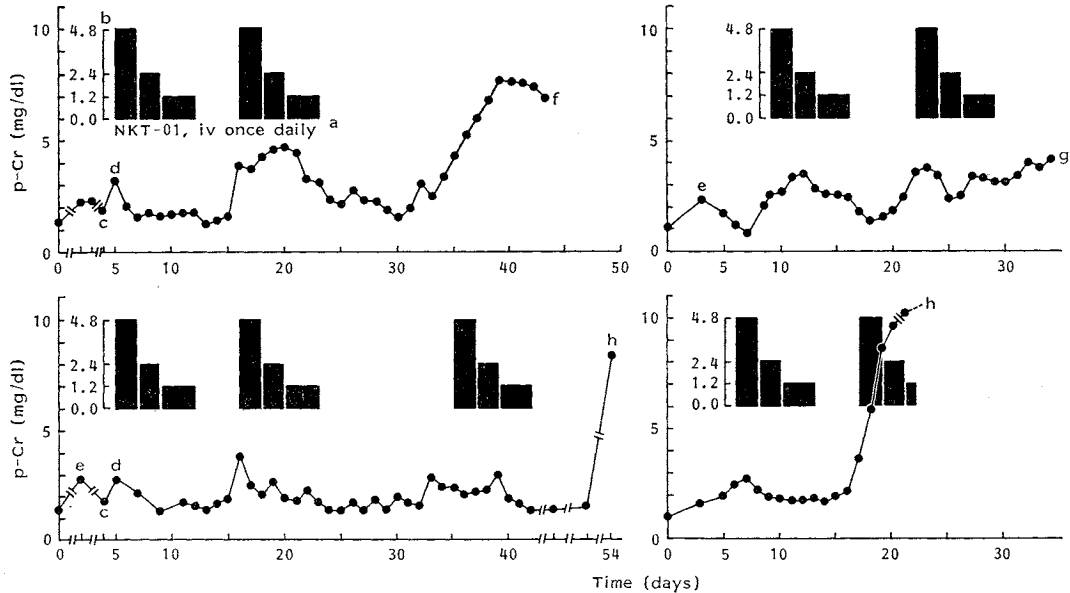


Fig. 2. Serial changes of plasma creatinine (p-Cr) levels after allogenic renal transplantation in dogs treated with NKT-01.

a) From the day of rejection onset, NKT-01 was administered intravenously as a rescue treatment for rejection at a dose of 4.8 mg/kg/day for the first two days, 2.4 mg/kg/day for the next two days and 1.2 mg/kg/day for the last three days, b) dosage of NKT-01, mg/kg, c, d) p-Cr levels in the morning and afternoon of 5th postoperative days, respectively, e) a rise of was due to the transient renal dysfunction related to grafting, f) moribund sacrificed, g) sacrificed, h) died.



Serial p-Cr changes after the operation in control dogs ( $n=6$ ) are shown in Fig. 1. An acute and irreversible rise of p-Cr was observed on the 6th to 9th postoperative day (p.o.d.) and all animals had either been moribund-sacrificed or died by the 12th to 22nd p.o.d. Severe rejection-related lesions of the kidneys such as hemorrhage, edema and mononuclear cell infiltration were recognized by macroscopic and microscopic examinations. Serial p-Cr changes in four animals treated with NKT-01 are shown in Fig. 2. The initial onset of rejection occurred on the 5th to 9th p.o.d. In all animals during this rejection, p-Cr levels clearly decreased after commencing NKT-01 treatment. During the recurrent rejection NKT-01 also reversed p-Cr levels in three of four animals. On microscopic examination of the four NKT-01 treated animals, granulation tissues showing a recovery from disturbances due to immune responses were observed in the renal cortex together with cellular rejection features similar to the control group.

Canine renal allotransplantation has been used for the preclinical evaluation of immunosuppres-

sive agents.<sup>11,12</sup> Efficacies of antilymphocyte globulin and methylprednisolone which have been used for treating acute rejection in clinics have been also confirmed in this experimental model.<sup>13,14</sup> On the basis of these earlier findings, we evaluated the efficacy of NKT-01 in the treatment of acute renal allograft rejection in dogs, and found that NKT-01 clearly reversed the acute rejection episodes.

The efficacy of NKT-01 was also confirmed by histopathologic examinations. The experimental model used in this study has been reported to be a severe model for assessing the ability of drugs to reverse an acute rejection episode.<sup>13,15</sup> Taking into consideration the severity of this dog model together with the favorable results in this study, we expect NKT-01 to become a potent agent for treating acute rejection episodes in organ transplantation. In further studies, the efficacy of NKT-01 should be evaluated in a mode analogous to the clinical situation such as in combined treatments with corticosteroids, azathioprine or cyclosporin A.

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