Transplant Int (1992) 5 [Suppl 1]: S542–S543

TRANSPLANT
International
© Springer-Verlag 1992

RS-61443 reverses acute renal allograft rejection in dogs

K.-P. Platz[2], W. O. Bechstein[2], D. E. Eckhoff[1], D. A. Hullett[1], and H. W. Sollinger[1]

[1] Department of Surgery, University of Wisconsin School of Medicine, Madison, Wisconsin, USA
[2] Department of Surgery, Rudolf Virchow University Clinic, Berlin, Germany

Abstract. RS-61443 is a noncompetitive allosteric inhibitor of inosine monophosphate dehydrogenase. At blocks the proliferative response of T and B lymphocytes, prevents the generation of cytotoxic T cells, and inhibits antibody formation. This study was conducted to see whether or not RS-61443 can reverse acute renal allograft rejection in dogs. At was possible to reverse this process.

Key words: RS-61443 – Inosine monophosphate dehydrogenase – Renal allografts – Rejection – Reversing rejection

RS-61443, a morpholinoethyl ester and prodrug of mycophenolic acid (MPA) is a noncompetitive allosteric inhibitor of inosine monophosphate dehydrogenase. The drug blocks the proliferative response of T and B lymphocytes, prevents the generation of cytotoxic T cells [2], and inhibits antibody formation by selectively inhibiting the de novo pathway of guanosine nucleotide synthesis [1]. RS-61443 has been shown to prevent renal allograft rejection in dogs for more than 150 days when administered in combination with low-dose cyclosporine and prednisolone [4]. Morris et al. demonstrated that RS-61443 prevents rejection of cardiac allograft in rats, even if the start of treatment was delayed until 5 days after transplantion. This suggests that RS-61443 can reverse ongoing acute allograft rejection [4]. The purpose of this study was to test whether or not RS-61443 can reverse acute renal allograft rejection in dogs.

Materials and methods

Animals: Unrelated female mongrel dogs, weighing 20 to 25 kg, were used as donors and recipients. Anesthesia was introduced with 20 mg/kg of intravenous pentobarbital, and halothane was used for maintenance. Donor kidneys were dissected out through a midline incision and flushed with 200 ml of ice-cold 0.9% saline solution containing 2000 units of heparine. After flushing, the kidney was immediately transplanted into the right iliac fossa of an unrelated recipient by routine techniques. Bilateral nephrectomy was performed after graft transplantation. Dogs were killed if the creatinine level exceeded 8 mg/dl, or if they were moribund. Autopsy was performed in all dogs.

Treatment schedule: Baseline immunosuppression consisted of 10 mg/kg RS-61443, cyclosporine (CyA) 5 mg/kg, and prednisolone 0.1 mg/kg, each given daily p.o. (this combination therapy had been shown to be unsuccessful in preventing acute allograft rejection in canine renal allografts). On the day of the diagnosis of rejection the dogs received an increased dose of RS-61443 p.o. for 3 consecutive days (80 mg/kg b.i.d.), also starting on the day rejection was diagnosed. After 3 days, upon completion of rejection treatment, baseline immuosuppression was increased to RS-61443 20 mg/kg. The dosages of CyA and prednisolone were not altered. If the serum creatinine rose > 3.0 mg/dl, CyA was discontinued to avoid nephrotoxicity. Rejection was defined as a 50% or greater increase in serum creatinine relative to the lowest observed creatinine level (Fig. 1). RS-61443 was supplied as powder by Syntex (USA) Inc. It was suspended in carboxymethylcellulose vehicle (100 mg/ml). Cyclosporine was supplied as a gift from Sandoz Pharmaceuticals, East Hannover, New Jersey, as a commercial solution. Prednisolone tablets were obtained from Upjohn Inc., Kalamazoo, Michigan. Before the initiation of rejection treatment, a percutaneous kidney biopsy was performed to confirm the diagnosis; these specimens were taken serially after the completion of rejection treatment.

Results

All animals experienced acute rejection. The diagnosis of rejection was made on day 7.5 ± 2.6 days. Serum creatinine on the day of diagnosis of rejection was

Offprint requests to: Hans W. Sollinger, Department of Surgery, University of Wisconsin School of Medicine, 600 Highland Avenue, Madison, WI 53792, USA

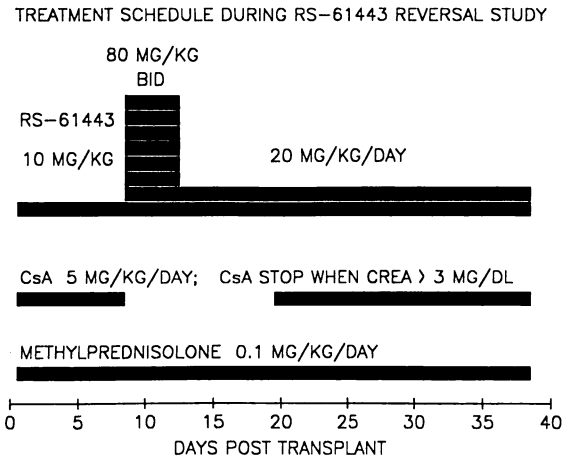

Fig. 1. Treatment of dog renal allograft rejection

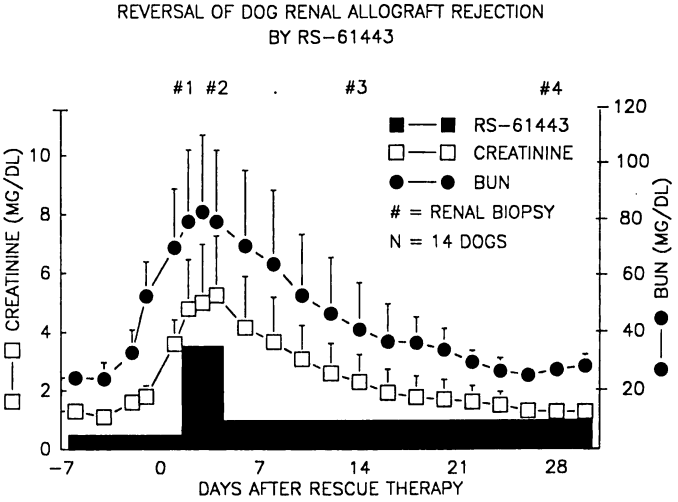

Fig. 2. Reversal of dog renal allograft rejection by RS-61443 (n = 14 dogs). Only in selected dogs were additional kidney biopsies performed at the intervals indicated *(# 2, # 3)*

3.6 ± 0.7 mg/dl. In 14 out of 16 dogs (87.5%), biopsy-proven acute cellular rejection could be successfully reversed by increasing the RS-61443 dosage to 80 mg/kg b.i.d.; however, it took up to 3 weeks after the diagnosis of rejection before serum creatinine and BUN returned to baseline levels (Fig. 2). Rejection treatment with increased doses of RS-61443 resulted in the development of severe, prolonged relative lymphopenia. Liver enzymes (AST, ALT) and alkaline phosphatase were slightly elevated. High-dose treatment with RS-61443 for 3 consecutive days was generally well tolerated. No weight loss or infectious complications occurred.

Discussion

RS-61443 had previously been shown to be effective in preventing kidney allograft rejection in dogs if used in combination with low-dose cyclosporine and prednisolone [4]. Reports of successful treatment of ongoing rejection of rat cardiac allografts [3] had prompted us to investigate the use of RS-61443 for reversal of kidney allograft rejection in dogs. Treatment with 80 mg/kg RS-61443 for established rejection of dog renal allograft could completely reverse rejection in 14 of 16 dogs (87.5%). In all of these 14 dogs, serum creatinine returned to baseline levels. High-dose treatment with RS-61443 for a period of 3 days was generally well tolerated in dogs. Intermittent loss of appetite and lassitude seemed to be related to the transient state of uremia. No weight loss or infectious complications occurred. Rejection treatment resulted in the development of severe, prolonged, relative lymphopenia. Liver enzymes (AST, ALT) and alkaline phosphatase were only slightly elevated, which are not necessarily signs of hepatotoxicity, but may rather be an indicator of mycophenolic acid effectiveness.

Acknowledgements. The support of Syntex Research, Palo Alto, California, is gratefully acknowledged. K.P. Platz and W.O. Bechstein received research fellowships from the Deutsche Forschungsgemeinschaft, Bonn, Germany.

References

1. Burlingham WJ, Grailer AP, Hullett DA, Sollinger HW (1991) Inhibition of both MLC and in vitro IgG memory response to tetanus toxoid by RS-61443. Transplantation 51: 545–547
2. Eugui EM, Almquist SJ, Muller CD, Allison AC (1991) Lymphocyte-selective antiproliferative and immunosuppressive effects of mycophenolic acid. Scand J Immunol 33: 161–173
3. Morris RE, Hoyt EG, Murphy MP, Eugui EM, Allison AC (1990) Mycophenolic acid morpholinoethylester (RS-61443) is a new immunosuppressant that prevents and halts heart allograft rejection by selective inhibition of T- and B-cell purine synthesis. Transplant Proc 22: 1659–1662
4. Platz KP, Sollinger HW, Hullett DA, Eckhoff DE, Eugui EM, Allison AC (1991) RS-61443: a new, potent immunosuppressive agent. Transplantation 51: 27–31