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RS-61443: successful rescue therapy in refractory renal rejection

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Abstract. RS-61443, the morpholinoethyl ester of mycophenolic acid (mPA), is a potent, noncompetitive, reversible inhibitor of eucaryotic inosine monophosphate (IMP) dehydrogenases. Because of the importance of the guanosine and deoxyguanosine nucleotides in activating phosphoribosyl pyrophosphate (PRPP) synthesis and ribonucleotide reductase, respectively, it was postulated that depletion of GMP (and consequently GTP and GDP) would have antiproliferative effects on lymphocytes. Furthermore, since lymphocytes rely on de novo pruine synthesis whereas other cell types do not, antiproliferative effects produced in this way are more selective for lymphocytes than other cell types.

Key words: Rescue therapy – RS-61443 – Renal rejection

RS-61443, the morpholinoethyl ester of mycopherolic acid (MPA), synthesized by Dr. peter Nelson (Syntex Research), was found to have improved bioavailability as compared with MPA [1]. Previous investigations, primarily in the laboratory of Dr. Anthony Allison and Dr. Elsie Eugui (Syntex Research), demonstrated that the drug blocks the proliferative responses of T- and B-lymphocytes [2] and inhibits antibody formation [3] and the generation of cytotoxic T-cells. In vivo monotherapy with RS-61443 was shown to prolong the survival of heart allografts in rats [4] and islet allograft survival in mice [5]. When combined with low doses of cyclosporine A (5 mg/kg) and prednisone (0.1 mg/kg), RS-61443 significantly prolonged the survival of renal allografts in mongrel dogs [6]. Furthermore, RS-61443 has the ability to reverse ongoing acute allograft rejection in a rat heart allograft model [4]. Recent experiments in our laboratory have further demonstrated that a short course of RS-61443 at 80 mg/kg b.i.d. reversed acute ongoing acute renal allograft rejection in 14 out of 16 dogs [7]. Based on these experimental data, a clinical trial was initiated in an attempt to evaluate the efficacy of RS-61443 for the reversal of acute refractory renal allograft rejection and evaluate the safety and tolerance to this drug.

In order to qualify for entry into this study, patients had to have refractory renal allograft rejection followed by at least one course of high dose steroids and OKT3.

Patients and methods

Thirty patients who had undergone cadaver renal allografts followed by induction therapy with quadruple immunosuppression (MALG, cyclosporin A, prednisone, azathioprine) and 8 patients who had received live donor kidneys followed by triple immunosuppressive therapy (cyclosporin A, prednisone, azathioprine) were entered into the study. Study entry requirements included biopsy-proven, therapy-resistant renal allograft rejection after at least one course of high dose steroid bolus therapy and at least one course of OKT3 therapy.

Table 1 demonstrates the mean number of high dose steroid and OKT3 courses in patients enrolled into the study. RS-61443 therapy was initiated at a dose of 2000 mg/day and was increased to 3500 mg/day when tolerated. At the initiation of RS-61443 therapy, azathioprine was discontinued. At 28 days after the initiation of the RS-61443 rescue therapy, a follow-up renal biopsy was obtained in all patients.

Results

In the living related donor group 6 grafts (75 %) were successfully rescued, while in the cadaver group, 20 grafts (66 %) were rescued. The mean rescue rate in both groups was 68 %. Among patients successfully rescued, a significant improvement in renal function was demonstrated, as shown in Table 2.

Table 1. Study population

	Steroid courses ($\bar{x}$)	OKT3 courses ($\bar{x}$)
Live donor ($n = 8$)	3.3	1.5
Cadaver donor ($n = 30$)	2.8	1.1

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Table 2. Improvement in renal function with RS-61443 rescue therapy

	Creatinine (mg%) (x̄) Start of therapy	Creatinine (mg%) (x̄) Now
Living donor	5.2 (2.7–10.3)	2.5 (1.4–4.2)
Cadaver donor	4.4 (2.3–11.2)	2.6 (1.0–4.0)

Table 3. Renal function after RS-61443 rescue therapy in comparison with initial creatinine level

	Creatinine > 5 mg%	Creatinine < 5 mg%
Rescue	6 (50%)	21 (81%)
Failure	6 (50%)	5 (19%)

Table 4. Side effects and complications

	No. of patients
Nausea/vomiting	4 (10%)
Diarrhea	4 (10%)
Cytomegalovirus (CMV)	3 (7.8%)
Leukopenia	2 (5%)
Loose stools	2 (5%)
CMV colitis	1 (2.5%)
Pancreatitis	1 (1.2%)
Hematuria	1 (1.2%)
Increased LFTs	1 (1.2%)

Successful rescue seemed to depend to a great degree on the serum creatinine level at which the patient was entered into the RS-61443 rescue protocol. As shwon in Table 3, 81% of the grafts were rescued when the patient was entered at a creatinine value below 5 mg%, while only 50% of the grafts were rescued when entered at a creatinine level above 5 mg%.

Significant side effects and complications of RS-61443 are listed in Table 4. Predominantly, the side effects related to the gastrointestinal system, such as nausea, vomiting, and diarrhea. Other complications such as cytomegalovirus (CMV) infection and leukopenia were associated with the therapy but could very well reflect the overall immunosuppressed state of the recipient, at least in part caused by prior antirejection therapy. In one patient, pancreatitis requiring discontinuation of RS-61443 seemed to have a clear relationship to the drug.

Discussion

This pilot rescue study demonstrated that RS-61443, even in therapy-resistant renal allograft rejection, has the ability to reverse or stabilize the rejection process. The failure or success of the rescue seems to depend largely on the degree of renal function at which therapy is initiated. In a few of the patients entered into this protocol, creatinine levels were above 9 mg%, and obviously the structural damage to the graft was irreparable at the time of initiation of rescue therapy. There were no life-threatening complications or major side effects, with the exception of gastrointestinal ones. The degree of nausea and vomiting, as well as diarrhea, may correlate with decreased absorption of the drug and may possibly explain the failure of the rescue therapy.

Of major interest in this study and the previous animal experiments in which ongoing acute allograft rejection was reversed is the possible mechanism by which an antiproliferative drug exerts this effect. For theoretical reasons, it seems unlikely that a drug which has solely antiproliferative effects is efficacious after clonal expansion of cytotoxic T-cells has already taken place. Therefore, an additional mechanism responsible for the rescue effect of RS-61443 is hypothesized. Recent data from the laboratory of Dr. Anthony Allison and Dr. Elsie Eugui provide a possible explanation (personal communication). In vitro studies have demonstrated that fucose and mannose are transferred through guanosine diphospho intermediates and dolicol phosphate. Mannose and fucose and their derivates are critical components of adhesion molecules. Allison and associates (unpublished observation) could demonstrate that in activated human peripheral blood lymphocytes, treatment with MPA significantly decreased the transfer of mannose to dolicol phosphate and to membrane glycoproteins, a process which is GDP-dependent.

In vitro studies show that one of the lymphocyte glycoproteins affected is VLA-4, the ligand for VCAM-1 on activated endothelial cells. Treatment of either B cells or IL-1-activated endothelial cells with MPA in therapeutically attainable doses decreased lymphocyte attachment, and when both cell types were treated with MPA, the attachment was further inhibited. If these findings can be extrapolated to the in vivo situation, treatment with MPA could decrease the recruitment of lymphocytes into sites of ongoing graft rejection and explain the rescue effects of RS-61443. At the current time, prospective, randomized trials are in progress to examine further the potential role of RS-61443 in the rescue therapy of therapy-resistant renal allograft rejections.

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