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RS-61443—A PHASE I CLINICAL TRIAL AND PILOT RESCUE STUDY[1]

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RS-61443, a morpholinoethyl ester of mycophenolic acid, inhibits the synthesis of guanosine monophosphate, which plays a pivotal role in lymphocyte metabolism. The drug blocks proliferative responses of T and B lymphocytes, and inhibits antibody formation and the generation of cytotoxic T cells. In vivo, RS-61443 prolongs the survival of islet allografts in mice, heart allografts in rats, and kidney allografts in dogs. Reversal of ongoing acute rejection was demonstrated in rat heart allografts and kidney allografts in dogs. Preliminary evidence suggests that the drug prevents chronic rejection.

The purpose of this study was to test the safety and tolerance in patients receiving primary cadaver kidneys. RS-61443 in doses from 100 mg/day p.o. to 3500 mg/day p.o. was given to patients in combination with cyclosporine and prednisone. Further study goals were to evaluate the pharmacokinetics of RS-61443, watch for the occurrence of opportunistic infections and acute rejection, and establish dosages for further clinical trials. Forty-eight patients were entered, with six patients in each dose group. RS-61443 was well tolerated in all dose groups, with only one adverse event possibly related to the drug (hemorrhagic gastritis). There was a statistically significant correlation between rejection episodes and dose (P=0.022), patients with rejection episodes versus dose (P=0.038), and number of OKT3/prednisone courses versus dose (P=0.008). There was no overt nephrotoxicity or hepatotoxicity. Preliminary results of a rescue trial in 20 patients with kidney transplants will also be presented.

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 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 purine synthesis, whereas other cell types do not, antiproliferative effects produced in this way are more selective for lymphocytes than other cell types. RS-61443, the morpholinoethyl ester of MPA synthesized by Dr. Peter Nelson (Syntex) was found to have improved bioavailability as compared with MPA (*1*). The drug blocks proliferative responses of T and B lymphocytes (*2*) and inhibits antibody formation (*3*) and the generation of cytotoxic T cells (*3*). 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 (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*) and in mongrel dogs who received unmatched kidney transplants (*7*). In the latter model, RS-61443 was found to be superior to steroid boluses (*7*). With the exception of gastrointestinal toxicity in dogs when administered at high doses (40 mg/kg), RS-61443 was well tolerated in experimental animals and did not exhibit nephrotoxicity, hepatotoxicity, or bone marrow suppression. Based on these in vivo experiments and extensive toxicology studies, a phase I clinical trial in renal transplantation was initiated. A pilot rescue study for patients who had previously undergone antirejection therapy with high-dose steroids and/or OKT3 was also initiated.

The purposes of this trial were: (1) to evaluate the safety of RS-61443 in doses ranging from 100 mg/day to 3500 mg/day; (2) to evaluate the pharmacokinetics of RS-61443; (3) to observe for the occurrence of opportunistic infections and acute rejection episodes; and (4) to establish dose levels of RS-61443 for future clinical trials. It was expected that some preliminary indications of efficacy might be gained during the study.

MATERIALS AND METHODS

This study is an open-label evaluation of RS-61443 as an immunosuppressant in patients receiving renal allografts. Forty-nine patients were entered into the study in eight dosing groups (100 mg/day to 3500 mg/day). One patient who died of an acute myocardial infarct on the first postoperative day was replaced. Six patients were entered into each group. The protocol was approved by the respective Institutional Review Boards (University of Wisconsin-Madison IRB 90-936-009; approved, University of Alabama IRB). Patients receiving between 100 mg/day and 1500 mg/day received the drug as a single dose. At higher doses, the drug was usually administered in two divided doses. Inclusion criteria were age 18 years or older, recipients of a first cadaveric renal transplant, and no known contraindication to the administration of cyclosporine, prednisone, or antilymphocyte globulin.

Immunosuppressive therapy consisted of prednisone 120 mg on the day of transplant surgery and for the next three days, followed by 30 mg per day for three months. From three months after transplantation

* Abbreviations: IMP, inosine monophosphate; MPA, mycophenolic acid; PRPP, phosphoribosyl pyrophosphate.

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to six months after transplantation, prednisone was tapered to 10 mg/day. Minnesota antilymphocyte globulin (MALG) 10–20 mg/kg was given for 14 days, starting on the first postoperative day. The drug was administered as a 6–8-hr intravenous infusion via a central line. Cyclosporine was administered once the serum creatinine fell below 3 mg/dl. Cyclosporine was administered between 6 and 12 mg/kg p.o., and was adjusted to maintain 24-hr trough levels of 350–500 ng/ml, as measured by whole-blood radioimmunoassay (*10*). Cyclosporine dosing was modified by the investigator as needed for renal toxicity or other adverse events. RS-61443 was substituted for azathioprine. Allograft rejection was treated with steroid bolus therapy in mild cases, or with OKT3 in steroid-resistant rejection, or as indicated by biopsy. Rejection episodes were usually confirmed by biopsy. In addition to clinical observation and assessment, laboratory determinations included CBC with differential blood count, platelet count, serum creatinine, BUN, SGOT, SGPT, calcium, phosphorus, total bilirubin, total protein, albumin, glucose, alkaline phosphatase, LDH, cholesterol, amylase, lipase, uric acid, chloride, CO_2, potassium, and sodium, and routine urinalysis.

Blood samples for pharmacokinetic assessments were obtained on days 1, 7, 14, and 20. On days 1 and 20 a full pharmacokinetic profile was obtained. On days 7 and 14, peak (1 hr post-dose) and trough levels were determined. Pharmacokinetic data determined included time to maximum concentration (T_{max} [hr]), maximum concentration (C_{max} [μg/ml]), and area under the curve (AUC) from 0 to 24 hr (μg/hr/ml). From April 17, 1990 to December 11, 1990, 48 patients were enrolled into this study. Patient age ranged from 19 to 67 years. Mean age was 43.3 years. The cumulative number of days on the drug ranged from 390 to 155 days. Patients were selected according to UNOS criteria (*11*). A detailed description of the patient population enrolled in the study is shown in Table 1. Causes of renal failure are shown in Table 2.

The pilot rescue study is an open-labeled, pilot, pharmacokinetic safety and efficacy study of RS-61443 for treatment of refractory cellular allograft rejection. The purpose of this study is to evaluate the efficacy of RS-61443 in doses of 2000 mg/day to 3500 mg/day in combination with other immunosuppressive agents for reversal of acute refractory cellular rejection in recipients of renal, hepatic, or cardiac allografts. Only recipients of renal allografts from the University of Alabama and the University of Wisconsin were included for preliminary analysis here. Inclusion criteria were patients with acute cellular rejection refractory to pulse steroids and/or adjunctive treatment with OKT3 and/or ALG.

TABLE 1. Patient population in ICM 1753

Age (years):	Mean 43.3 (range 19–67)
Sex:	
Male	30 (63%)
Female	18 (37%)
Race:	
Black	16 (33%)
White	30 (62%)
Hispanic	1 (2.5%)
Asian	1 (2.5%)
Dialysis:	
Yes	42 (88%)
No	6 (12%)
Transfused:	
Yes	33 (69%)
No	14 (29%)
Unknown	1 (2%)
Diabetes:	6 (13%)
0 MM:	2 (4%)
1 MM:	5 (10%)
3 MM:	19 (39%)
>3 MM:	22 (46%)

TABLE 2. Cause of renal failure in ICM 1753

Glomerulonephritis	17 (35.4%)
Hypertension	6 (12.5%)
Diabetes	6 (12.5%)
Polycystic kidney	6 (12.5%)
Congenital	3 (6.2%)
Pyelonephritis	2 (4.1%)
Atherosclerosis	1 (2.0%)
Hemolytic uremic syndrome	1 (2.0%)
Penicillamine	1 (2.0%)
Unknown	5 (10.8%)

TABLE 3. Infections—serious adverse effects in ICM 1753

Group I (100 mg/day)	1 CMV gastritis
	1 Clostridium difficile colitis
Group II (250 mg/day)	1 CMV
Group III (500 mg/day)	None
Group IV (1000 mg/day)	1 Hemorrhagic gastritis
Group V (1500 mg/day)	3 Mild ileus
Group VI (2000 mg/day)	1 Wound infection
	1 CMV gastritis
Group VII (3000 mg/day)	1 *Candida* esophagitis
	2 CMV
Group VIII (3500 mg/day)	1 Esophagitis
	2 Nausea and vomiting

RESULTS

Five patients did not complete the study for the following reasons: one was unable to comply with the protocol; one had prolonged ATN; one had hemorrhagic gastritis; one had a technical graft loss secondary to venous thrombosis; and one had a graft loss secondary to hemolytic uremic syndrome. The patient who was excluded because of prolonged ATN was a patient in the 500 mg/day group. This was done at the investigator's request, and not because RS-61443 was thought to contribute to ATN.

In general, the drug was well tolerated, and there was only one serious adverse event that we thought could be related to RS-61443. This patient in the 1000 mg/day group developed hemorrhagic gastritis, diagnosed by endoscopy. After discontinuation of RS-61443 and intensive treatment with H-2-blockers and antacids, the patient recovered, and no further adverse events were noted. As seen in Table 3, infectious complications and serious adverse effects were rather equally distributed among dose groups, and no obvious increase in adverse events or infectious complications was seen in the higher dose ranges.

Pharmacokinetic studies demonstrated that serum concentration as well as AUC was significantly lower in the initial interval after transplantation compared with day 20 after transplantation (Fig. 1). Table 4 summarizes the pharmacokinetic data obtained from the study. It should also be noted that there was substantial variation among individual patients.

While the primary purpose of this study was to test the safety and tolerance of RS-61443 and obtain pharmacokinetic data, a preliminary analysis was carried out to test its efficacy as an immunosuppressive agent. In both participating centers, the incidence of rejection episodes declined with increasing doses of RS-61443 (Fig. 2), and significantly fewer patients had rejection episodes at dose levels of 2000 mg/day and above (Fig. 3). As a measure of the severity of rejection episodes, the

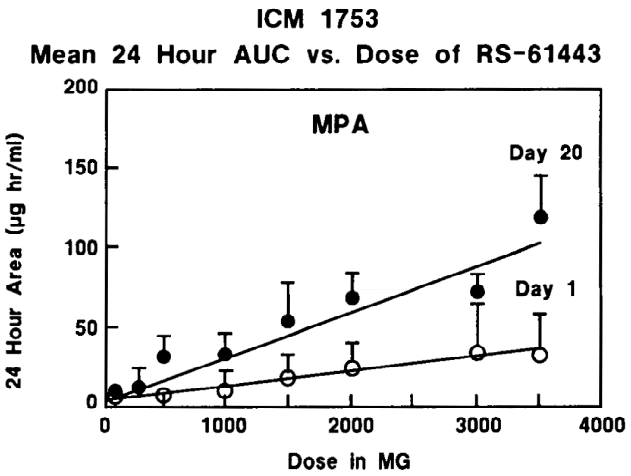

FIGURE 1. Serum concentrations of MPA on day 1 and day 20 posttransplantation for dose groups from 100 mg/day p.o. to 3500 mg/day p.o.

TABLE 4. Pharmacokinetics of MPA in renal transplant patients following oral administration of RS-61443 (mean ± SD)

Dose of RS-61443	Day 1				Day 20			
	n	T_{max} (hr)	C_{max} (µg/ml)	AUC (0–24) (µg/hr/ml)	n	T_{max} (hr)	C_{max} (µg/ml)	AUC (0–24) (µg/hr/ml)
100 mg q.d.	5	6.3 (8.1)	1.0 (0.2)	0.9 (1.8)	6	0.8 (0.3)	2.0 (1.0)	3.3 (3.2)
250 mg q.d.	6	2.3 (1.3)	2.1 (2.1)	7.1 (10.9)	6	3.0 (5.0)	4.3 (2.3)	7.7 (2.9)
500 mg q.d.	6	5.2 (4.1)	1.1 (0.6)	6.4 (3.5)	6	0.8 (0.6)	5.9 (2.4)	24.0 (16.8)
1000 mg q.d.	3	6.7 (2.3)	1.6 (0.9)	10.4 (8.1)	5	0.7 (0.3)	9.1 (2.1)	24.1 (8.6)
1500 mg q.d.	6	10.0 (9.6)	2.5 (2.6)	18.1 (11.7)	6	0.9 (0.2)	10.8 (6.2)	49.8 (18.9)
1000 mg b.i.d.	6	6.1 (4.8)	2.6 (2.5)	24.6[a] (11.2)	6	1.6 (1.3)	8.2 (3.6)	65.4[a] (10.9)
1500 mg b.i.d.	5	9.6 (3.6)	5.1 (6.2)	39.0[a] (27.8)	4	1.1 (0.6)	13.0 (8.4)	73.2[a] (10.3)
1750 mg b.i.d.	6	4.8 (4.3)	3.2 (3.5)	37.6[a] (18.9)	6	1.3 (0.8)	18.7 (12.2)	119.0[a] (13.9)

[a] 24-hr area based on two times the 12-hr area.

frequency of treatment with high-dose steroids and/or OKT3 was correlated with the dose of RS-61443 (Fig. 4).

Detailed laboratory investigations did not reveal any evidence of bone marrow suppression. Patients in all dose groups had near-normal white cell counts, and in no instance was the drug discontinued for leukopenia. Similarly, no significant sustained elevations in liver functions were seen, despite the fact that occasional patients had temporary elevations in LDH and GGT. In a few patients, mild elevation in serum lipase was noted—however, this was usually not associated with elevated serum amylase, and no clinical evidence of pancreatitis was evident. As demonstrated in Figure 5, no evidence of overt nephrotoxicity was seen. Serum creatinine values at higher dose ranges, in fact, were lower, and this might be due to the lower incidence of rejection episodes and consequent decrease in damage to the kidney. With the exception of the previously

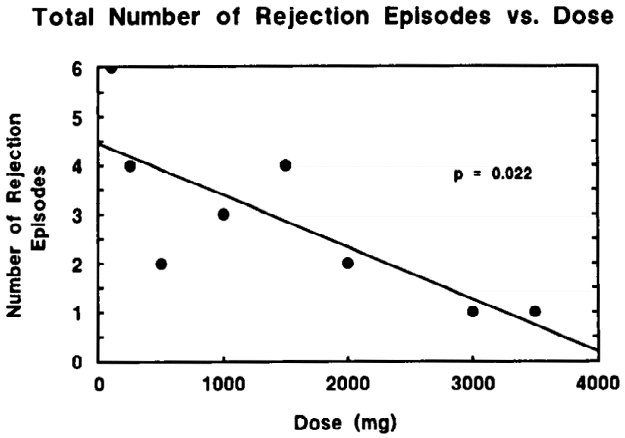

FIGURE 2. Correlation of total number of rejection episodes with and dose of RS-61443.

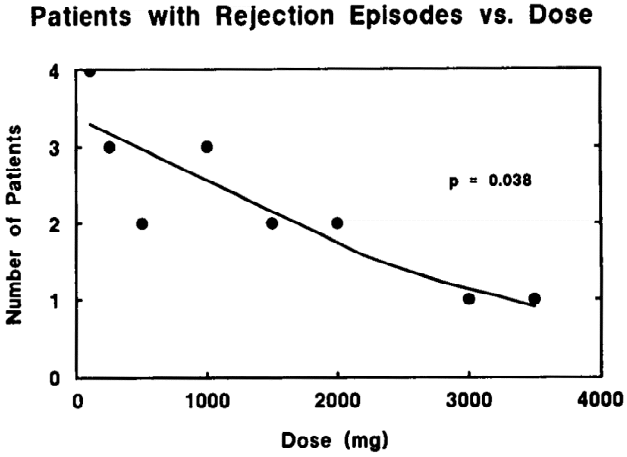

FIGURE 3. Correlation of rejection episodes with dose of RS-61443.

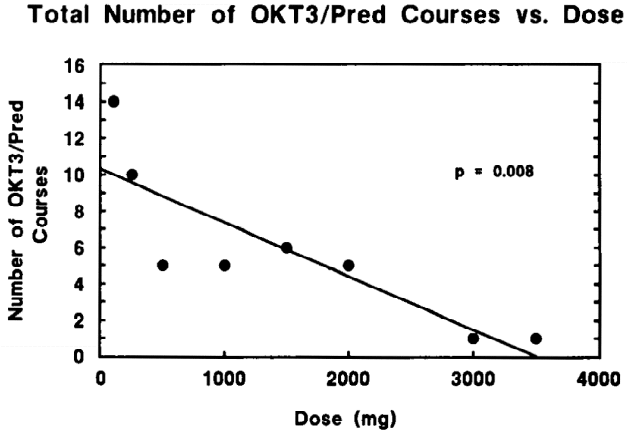

FIGURE 4. Correlation of total number of OKT3 with prednisone courses versus dose of RS-61443.

mentioned patient with prolonged acute tubular necrosis, no patients required discontinuation of the drug. There did not appear to be any neurotoxicity or hypertension related to RS-61443. As mentioned above, the incidence of severe rejections

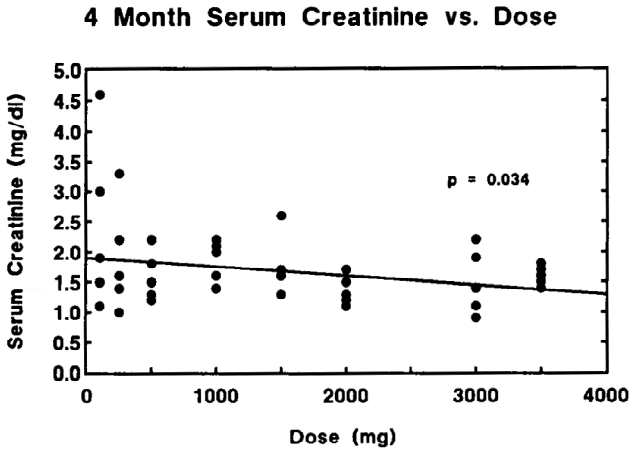

FIGURE 5. Correlation between serum creatinine four months after transplantation and dose of RS-61443.

decreased significantly with increasing doses of RS-61443, and all rejections in the higher-dose groups were easily reversed.

From December 10, 1990 to May 1, 1991, a total of 21 patients were enrolled into a pilot study of RS-61443 for treatment of refractory allograft rejection. As defined by the protocol, patients had to have biopsy-confirmed, refractory acute cellular rejection. The majority of these patients had undergone several courses of antirejection therapy, including high-dose steroid boluses and OKT3. Among the recipients analyzed, five had received living-donor kidney transplants and fifteen cadaver donor kidney transplants. In the LRD group, rejection was reversed in four of five patients, and in the CAD group, rejection was reversed in seven of fifteen patients. In five patients in the CAD group, creatinine improved or stabilized. One graft in the LRD group and three grafts in the CAD group failed, and the patients returned to dialysis. The patients were entered into the study with creatinine values of 11.3, 9.6, and 9.5, respectively. The failure of achieving reversal of rejection in these patients was probably due to the late initiation of RS-61443 rescue therapy. It is likely that the grafts had already sustained irreparable structural damage. A more complete report of these refractory rejection patients will be forthcoming.

DISCUSSION

Over the past three years, the field of transplantation has witnessed an explosion in the development of new immunosuppressive compounds. In addition, several more are currently under development by a number of pharmaceutical companies, and a battery of new monoclonal antibodies will soon be tested in clinical trials. While the majority of these drugs are excellent in preventing cell-mediated graft rejection, they do not equally inhibit the long-term humoral immune responses mediated by antibodies and directed against the alloantigen of the donor, which may mediate chronic rejection. Because of the interest of one author's (HWS's) laboratory in the role of antibodies in sensitized patients and chronic rejection, we were intrigued by the potential of RS-61443 for down-regulating antibody responses, and we were delighted to have an opportunity to participate in the preclinical development and in the initiation of the described clinical trials.

In our initial experience in dogs, it became obvious that the drug is a very potent immunosuppressive agent—however, monotherapy at a dose of 40 mg/kg/day p.o. was associated with significant gastrointestinal toxicity and graft survival did not exceed 45 days. Therefore, the dose of RS-61443 was lowered to 20 mg/kg/day p.o. and combined with low doses of cyclosporine and prednisone. We have chosen low doses because ultimately our clinical goal is to use RS-61443 in a manner that allows reduction of cyclosporine and prednisone to reduce toxicity and side effects. Using this protocol, more than 50% of the dogs had grafts surviving for more than 150 days.

These considerations went into the design of the current clinical trial. RS-61443 was substituted for azathioprine and combined with cyclosporine and prednisone. Using increasing doses of RS-61443, we would obtain information about the safety of the drug, and we hoped that some information about efficacy could be gained. In addition, a further goal was to collect pharmacokinetic data. All these goals were achieved. Pharmacokinetic evaluation demonstrated relatively low plasma levels of MPA when administered immediately after transplantation. A steady state is achieved at about 7 days after the start of dosing. The cause of this observation is unclear, as patients treated with RS-61443 for mild cardiac allograft rejection achieved higher levels much sooner (Syntex Research, unpublished data). The possibility that the drug is absorbed at a slower rate in uremic patients needs to be examined. Furthermore, intensive antacid therapy in the perioperative period may alter drug absorption. It is also possible that altered metabolism of MPA occurs, as levels of MPA glucuronide were close to values observed in patients who had not recently had surgery. The effect of T_{max}, C_{max}, and AUC on graft survival is currently being analyzed, and these results may add to further refinement in drug dosing and administration.

Clearly, the most significant observation during this study was the obvious lack of major adverse events and/or toxicity related to RS-61443. We thought that only 1 in 48 patients had an adverse effect that could possibly be related to RS-61443. While there was a significantly reduced incidence in the number and severity of rejections with increased doses of RS-61443, further prospective, randomized, double-blind trials will be initiated to substantiate these early observations.

The most surprising aspect of the experimental work with RS-61443, as well as the early results of this study, was the observation that RS-61443 is able to reverse an already ongoing allograft rejection. The first data suggesting such an effect were reported by Morris' group in a heart allograft model (*4*). The investigators delayed the administration of RS-61443 until the fifth day following transplantation, by which time there was a marked mononuclear cell infiltrate into the graft and edema. Reversal of rejection was demonstrated functionally and histologically. When azathioprine or cyclosporine was given under comparable conditions, rejection could not be prevented. Platz et al. (*7*), from our own laboratory, confirmed these findings in acute renal allograft rejection in dogs. Three doses of RS-61443 (80 mg/kg b.i.d.) reversed ongoing acute allograft rejection in 14 of 16 animals. In comparison, steroid bolus therapy under identical conditions could only temporarily halt rejection in some dogs, but eventually, all animals lost their grafts within 20 days. Initially, the mechanism underlying these observations was poorly understood, as a drug which inhibits proliferative events should not be effective once specific effector cells have already been generated. Most recently, however, in vitro data

from Allison's laboratory has provided a possible explanation. The authors argue that there is substantial evidence that mannose, fucose, and their derivates are critical components of several adhesion molecules. Fucose and mannose are transferred through guanosine diphospho- intermediates and dolicol phosphate. Allison and his associates 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 that is GDP-dependent. In vitro studies showed that one of the lymphocyte glycoproteins affected is VLA-4, the ligand for V-cam-1 on activated endothelial cells. Treatment of either T 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 (Allison A, personal communication).

If these findings can be extrapolated to the in vivo situation, treatment with MPA could decrease recruitment of lymphocytes into sites of ongoing graft rejections. Therefore, inhibition of adhesion molecule glycosylation may contribute to the efficacy of RS-61443 in the treatment of ongoing rejection under conditions in which clonal expansion has already occurred.

In summary, these clinical trials have provided useful information regarding the efficacy of RS-61443 in the prevention and treatment of renal allograft rejection. While much has to be learned about this new and exciting drug, it seems clear at this juncture that the drug is well tolerated and seems to lack major toxicity. Prospectively randomized trials are being designed to fully investigate the potential future role of RS-61443.

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Drs. Anthony Allison and Elsie Eugui (Syntex Research), who discovered and analyzed the immunosuppressive effect of RS-61443.

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ORAL DISCUSSION

DR. R. MORRIS (Stanford, California): Since we know that RS-61443 directly inhibits B cell proliferation, do you test your patients to determine whether immunological memory has been erased for certain recall antigens?

DR. SOLLINGER: I have only some experimental evidence and some anecdotal experience in patients. At this time it does not look like the drug will down-regulate antibodies against class I antigens. It must be emphasized that this is very preliminary information.

DR. GONWA (Dallas, Texas): We have treated five patients in a renal transplant rescue trial, and our results were very similar to yours. We have also treated about 10 liver recipients with excellent results in a rescue protocol. We did have one patient who developed leukopenia that reversed when we lowered the dose of the drug. We have had three other patients who complained of proximal muscle weakness, particularly in the thighs. That too seemed to reverse when we lowered the dose of drug. Have you made similar observations?

DR. SOLLINGER: We haven't seen the muscle weakness. We have seen several patients with leukopenia; in each instance, the leukopenia was associated either with CMV infection or the administration of glanciclovir or high-dose aciclovir. Dr. Tony Allison has suggested the potential existence of a drug interaction between glanciclovir or aciclovir and RS-61443. I should explain that in all cases, the white cell count returned to normal after the RS-61443 dose was reduced.

DR. JORDAN (Pittsburgh, Pennsylvania): Did you notice differences in cyclosporine levels between your different dosage groups? Could that possibly have an influence on the incidence of rejection in the different groups?

DR. SOLLINGER: There was no obvious difference, but again these are preliminary conclusions. If anything, cyclosporine doses were somewhat lower, but levels seemed quite comparable.

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