RS-61443 (Mycophenolate Mofetil)

A Multicenter Study for Refractory Kidney Transplant Rejection

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RS-61443 (mycophenolate mofetil) inhibits a key enzyme fo the *de novo* synthesis of purine nucleotides in T and B lymphocytes. The purpose of this study was to evaluate the efficacy of RS-61443 in patients with refractory renal allograft rejection. Patients eligible for the study had previously undergone anti-rejection therapy with high-dose steroids or OKT3 monoclonal antibody. All rejection episodes were proven by renal biopsy. Successful rescue was achieved in 52 (69%) patients. Rescue was more successful when patients were entered with a creatinine of 4 mg/dL or lower (79%), *versus* a 52% rescue rate in patients entered with a creatinine of 4 mg/dL or above. Major side effects were predominantly gastrointestinal, but there was no overt nephrotoxicity, hepatotoxicity, or bone marrow suppression. The overall infection rate was 40%, with the spectrum of infections characteristic for the highly immunocompromised patient. The conclude that this pilot study suggests that RS-61443 is effective in refractory kidney allograft rejection. Based on this study, prospectively randomized multi-center trails have been planned and are in progress.

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RS-61443 (MYCOPHENOLATE MOFETIL), a morpholinoethyl ester of mycophenolic acid (MPA), is a potent, noncompetitive, reversible inhibitor of eucariotic inosine monophosphate dehydrogenases. Because of the importance of guanosine and deoxyguanosine nucleotides in activating phosphoribosil pyrophosphate synthesis and ribonucleotide reductase, respectively, it was postulated that depletion of guanosine monophosphate (and consequently, guanosine triphosphate and guanosine diphosphate) would have antiproliferative effects on lymphocytes. Furthermore, because 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 synthesized by Dr. Peter Nelson (Syntex Corporation, Palo Alto, CA) was found to have improved bioavailability as compared with mycophenolic acid. *In vivo,* the drug blocks proliferative responses of T and B lymphocytes[1] and inhibits antibody formation[2] and the generation of cytotoxic T-cells.[2] *In vivo,* monotherapy with RS-61443 was shown to prolong the survival of heart allografts in rats and islet allograft survival in mice.[3,4] 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.[5]

The first clinical trials with RS-61443 were conducted at the University of Wisconsin-Madison and the University of Alabama-Birmingham.[6] 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 orally to 3500 mg/day orally was given to patients in combination with cyclosporine and prednisone. 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. There was a statistically significant correlation between rejection episodes and dose, patients with rejection episodes *versus* dose, and number of OKT3/prednisone courses *versus* dose. There was no overt nephrotoxicity

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of hepatotoxicity. Although the above-described experiments, as well as the phase I clinical trial, seemed to indicate the potential promise of RS-61443 in maintenance therapy, animal experiments performed by Morris et al.[7] and our own group[8] suggested that the drug might also be efficacious for the treatment of acute allograft rejection. Morris et al.[7] demonstrated complete reversal of histologically established acute heart allograft rejection. The investigators delayed the administration of the drug until several days after transplantation. At a point when a heavy lymphocytic infiltrate was demonstrated in the myocardium in control experiments, initiation of RS-61443 therapy resulted in a reversal of the rejection process. Platz et al.[8] from our laboratory confirmed these experiments in a dog renal allograft model. Mongrel dogs receiving a renal allograft were treated with low-dose baseline immunosuppression consisting of RS-61443 (10 mg/kg), cyclosporine (5 mg/kg), and prednisone (0.1 mg/kg). After the animals started to reject their grafts as indicated by a significant rise in serum creatinine as well as biopsy-confirmed histologic diagnosis, anti-rejection therapy was instituted. In one group, animals received a high-dose steroid bolus for 3 days, whereas in the other group, a 3-day bolus of 80 mg/kg of RS-61443 was administered orally. Steroid bolus therapy was only able to temporarily halt the rejection process, and ultimately, all animals lost their grafts within 20 days. In contrast, 14 of 16 dogs treated with a 3-day RS-61443 bolus had reversal of the rejection process, and within 20 days, serum creatinine returned to pre-rejection levels. These observations provided the stimulus to initiate this pilot rescue study.

Materials and Methods

This pilot study was designed as an open-label study of RS-61443 as an immunosuppressant for treatment of acute refractory cellular allograft rejection. By definition, the rejection must have been proven by biopsy and must have been refractory to treatment with at least one course of ALG/OKT3, whether or not the patient has received high-dose steroids. Also eligible were patients with re-rejection who were unable to tolerate further courses of OKT3 or ALG. Concomitant treatment with maintenance doses of cyclosporine and prednisone were permitted, but all other immunosuppressive drugs were prohibited during treatment with RS-61443. Dosing with RS-61443 was initiated within 48 hours of the kidney biopsy. Patients were treated with 1000 to 1500 mg of RS-61443 twice a day.

TABLE 1. *Patient Characteristics (n = 75)*

Type of transplant	
LRD	11 (15%)
LURD	3 (4%)
CAD 1	50 (66%)
CAD 2	11 (15%)
Sex	
Male	45 (60%)
Female	30 (40%)
Age (yr)	Mean 37 (range 8–68)
Race	
White	41 (55%)
Black	26 (35%)
Hispanic	5 (7%)
Asian	2 (2%)
Filipino	1 (1%)

TABLE 2. *Histocompatibility Data*

	Total Mismatch		PRA Pretransplant	
	Mean	Range	Mean	Range
LRD	3 (50%)	0–6	3	0–21
LNR	4.33 (72%)	3–6	1	0–3
CAD 1	3.72 (62%)	0–6	8.38	0–71
CAD 2	3.5 (58%)	0–6	14	0–63

Exclusion criteria included pregnant women, nursing mothers, patients with severe infections requiring antimicrobial therapy at the time of entry into the study, and patients with a white blood count <2000/mm^3, platelet count <50,000/mm^3, or hemoglobin <8 g/dL. Also excluded were patients with active peptic ulcer disease. Furthermore, patients with severe diarrhea or ileus that might interfere with their ability to absorb oral medication were excluded.

Five centers (University of Wisconsin, Madison, WI; University of Alabama-Birmingham, Birmingham, AL; UCSF Medical Center, San Francisco, CA; UCLA Medical Center, Los Angeles, CA; Baylor University Medical Center, Dallas, TX) participated in the study after approval of the individual institutional review boards was obtained.

Although the induction immunosuppressive protocol in the participating institutions differed, there was agreement regarding the desired cyclosporine maintenance levels. All institutions attempted to achieve whole blood serum levels as monitored by TDX to be between 300 and 500 ng/mL. First rejection episodes were generally treated with intravenous steroid boluses (250 to 500 mg IV/day) followed by tapering oral steroid doses. Depending on the severity of second or subsequent rejection episodes, repeat steroid boluses were used or OKT3 therapy was instituted. In all participating centers, OKT3 was used if re-rejection occurred after completion of the initial steroid regimen or if breakthrough rejection occurred during steroid tapering. Furthermore, the decision to use OKT3 was also based on the severity of rejection determined by biopsy.

A total of 75 patients were enrolled between December 10, 1990 and September 16, 1991. Patient characteristics are shown in Table 1. Degree of mismatch as well as pretransplant panel reactive antibodies is shown in Table 2.

TABLE 3. *Treatment of Rejection Before RS-61443 Therapy*

	No. of Prednisone Courses Prestudy		OKT3/ALG Courses Prestudy	
	Mean	Range	Mean	Range
LRD	3	1–6	1.64	1–2
LNR	2.33	0–5	1.0	1
CAD 1	2.34	1–9	0.98	0–2
CAD 2	1.64	0–4	1.1	1–2

Results

Among the 75 patients enrolled in the study who were qualified for entry into the rescue study, all but two had received both high-dose steroids and OKT3 before study entry. In all cases, a biopsy within 48 hours of initiation of RS-61443 rescue therapy demonstrated acute cellular rejection. The mean number of high-dose steroid courses, as well as OKT3 or ALG courses, is shown in Table 3.

Successful long-term rescue was achieved in 52 (69%) of patients (Table 4). Successful rescue was defined as stabilization or improvement of renal function. Follow-up time of successfully rescued patients now ranges from 6 to 15 months. The success of rescue therapy was related to the quality of renal function at the time of the start of RS-61443 therapy. Patients enrolled with a serum creatinine of 4.0 mg/dL or less had a rescue rate of 79%, whereas patients enrolled with a serum creatinine of 4 mg/dL or greater had only a 52% rescue rate (Table 5). Successfully rescued patients who have remained on RS-61443 demonstrated continued improvement in renal function over the entire study period (Table 6).

A typical post-transplant course for one of the patients enrolled in the rescue study is shown in Figure 1. Patient CT, after receiving a first cadaver kidney transplant, had several rejection episodes treated with multiple steroid boluses and two courses of OKT3. After the second course of OKT3, her renal function deteriorated again and RS-61443 rescue therapy was initiated. Over a follow-up period of 1 year, her serum creatinine has improved to 1.2 mg/dL, and she had no further rejection episodes. Renal biopsy the day before RS-61443 is shown in Figure 2. Protocol biopsy on day 28 after RS-61443 was started is shown in Figure 3.

In 19 patients, the drug was discontinued for treatment failures. In these patients, allograft rejection could not be reversed, and the patients either had to return to dialysis or underwent transplant nephrectomy. In 11 patients, RS-61443 therapy was discontinued for other reasons than treatment failures (Table 7). Reasons that definitely are not associated with the use of RS-61443 include one ureteral leak, one death, most likely due to a cardiac event, one cancer in the native kidney that was not recognized before transplantation, and two cases of recurrent glomerulopathy. Reasons for discontinuation probably related to the drug were one case of pancreatitis, one case of cytomegalovirus colitis, and two cases of gastrointestinal complications.

Infections during RS-61443 rescue therapy were common and represent the overall spectrum of infections in the highly immunocompromised patient (Table 8). No patient died of infectious complications.

Side effects of RS-61443 were predominantly gastrointestinal complaints (Table 9). Nausea and diarrhea were most commonly observed at the initiation of RS-61443, and in most instances were self-limiting or responded to dose reduction. In several patients, three times a day administration was better tolerated than twice-daily administration. The only severe gastrointestinal side effects occurred in one patient with pancreatitis, and in a second patient with hemorrhagic gastritis. In both patients, discontinuation of RS-61443 treatment resulted in a resolution of symptoms. Leukopenia was frequently associated with cytomegalic virus infection or treatment with ganciclovir. Allison and associates (personal communication) have postulated a drug interaction between RS-61443 and ganciclovir resulting in leukopenia. Leg pain, weakness, and myalgia, interestingly, were only observed in one participating center. Other side effects were nonspecific, and were not clearly related to RS-61443. During the study period, no evidence of significant nephrotoxicity, hepatotoxicity, or bone marrow suppression was observed.

TABLE 4. *Successful Long-term Rescue (n = 75)*

LRD	5 (45%)
LURD	3 (100%)
CAD 1	39 (78%)
CAD 2	5 (45%)
Total	52 (69.0%)

TABLE 5. *Timing of Rescue*

	Successful Rescue
Creatinine >4.0 mg/dL	52%
Creatinine ≤4.0 mg/dL	79%

TABLE 6. *Mean Creatinine Levels of Study Patients*

	Creatinine Pre-RS-61443		Creatinine Day 28		Creatinine Day 56		Current Creatinine	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
LRD	4.65	3.1–8.8	3.10	1.7–5.9	3.10	1.1–4.9	2.62	1.4–3.5
LNR	2.50	1.7–3.6	2.10	1.6–2.7	2.03	1.5–2.3	1.83	1.4–2.1
CAD 1	3.74	1.5–9.8	2.98	1.2–5.9	2.78	1.0–7.5	2.44	1.2–5.8
CAD 2	5.35	2.1–11.3	2.50	1.3–4.3	2.78	1.4–5.6	2.22	1.6–2.4

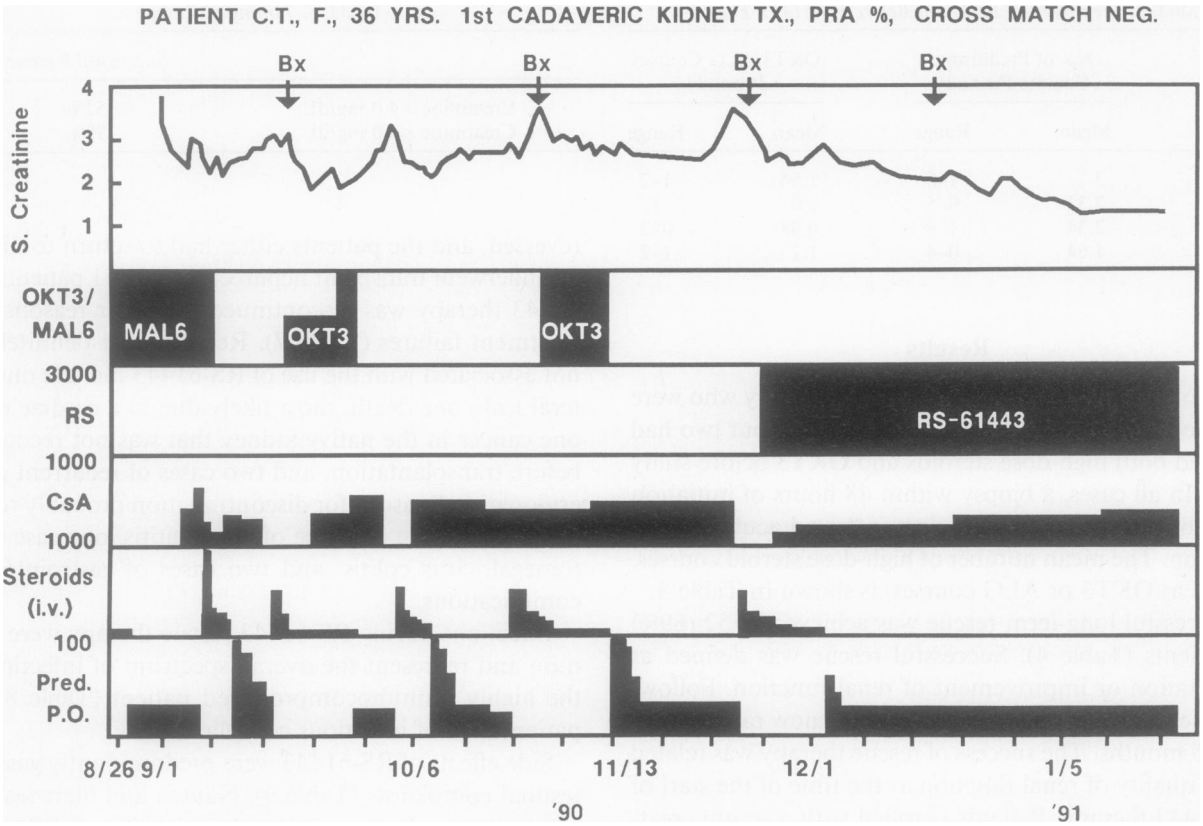

FIG. 1. Typical course for a patient enrolled in RS-61443 rescue study.

Discussion

Based on animal experiments from our own laboratory[8] and the report of Morris et al.,[7] we felt encouraged to test the potential of RS-61443 in reversing acute allograft rejection. Because other agents such as high-dose steroids and OKT3 are extremely useful in the treatment of acute allograft rejection, the investigators believed that a protocol that addresses refractory renal allograft rejection after extensive treatment with high-dose steroids and OKT3 would be the appropriate pilot study to gain some initial information about this drug's potency. The study was designed with the intent to use RS-61443 for rescue therapy after conventional anti-rejection therapy had failed. With

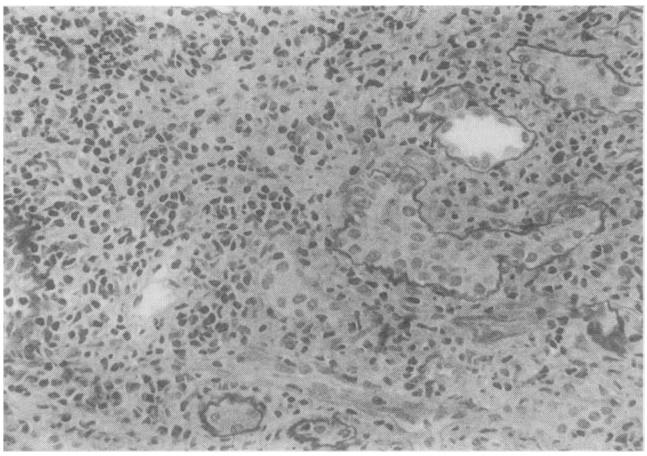

FIG. 2. Biopsy before initiation of RS-61443 rescue therapy. The interstitium shows moderate to severe infiltration by lymphocytes. Tubules show focal injury.

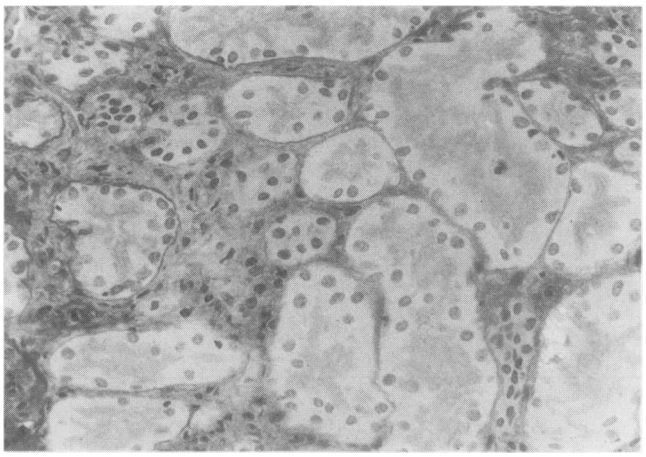

FIG. 3. Biopsy 28 days after initiation of RS-61443 therapy. The interstitial lymphocytic infiltrate is significantly decreased. Mild chronic tubular interstitial nephritis remains.

TABLE 7. *Patients Terminated From Study for Nontreatment Failure (n = 11)*

Recurrent disease	2
Lymphoma	2
Pancreatitis	1
Death (unknown cause)	1
Ureteral leak	1
CMV colitis	1
GI bleed	1
GI side effects	1
CA native kidney	1

the exception of two patients in this study, all patients had received both high-dose steroid therapy and OKT3. Despite the rather advanced state of rejection in some patients with serum creatinine levels above 9 mg/dL, we were able to reverse rejection in 69% of patients. It was also shown that earlier intervention with RS-61443 resulted in a higher rescue rate (79%). Clearly, in some of our patients, renal damage was so extensive that even a reversal of the immunological event left us with an organ beyond repair. Patients undergoing multiple rejection episodes and treatment with multiple doses of high-dose steroids and OKT3 represent a group that is highly susceptible to complications of immunosuppressive therapy, particularly infections. Therefore, the infection rate of 40% in our group is within expectation. Clearly, a high incidence of cytomegalovirus infection, as well as herpes infections, must be expected. It is encouraging, however, that none of the patients in this rescue group died from the complications of infection.

Side effects, as expected, were mainly gastrointestinal in nature. In most patients, mild nausea, occasional vomiting, and diarrhea was observed. These side effects were either self-limiting or responded to dose reduction. The two most severe gastrointestinal complications included pancreatitis and hemorrhagic gastritis. In both cases, symptoms resolved after drug discontinuation. Other side effects observed were listed for the sake of completeness; however, no clear-cut relationship to RS-61443 was demonstrated. This view is supported by the fact that in more than 350 patients receiving RS-61443 for the treatment of therapy-resistant rheumatoid arthritis, none developed infectious complications.

TABLE 8. *Infections*

CMV	13 (17%)
Oral/GI candida	7 (9%)
Herpes zoster	3 (4%)
Herpes simplex	2 (3%)
C. difficile	1 (1%)
E. coli (systemic)	1 (1%)
Listeria	1 (1%)
Pneumocystis	1 (1%)
Bacterial pneumonia	1 (1%)
Overall infection rate	30/75 (40%)

TABLE 9. *Side Effects*

Moderate GI	17
Mild GI	13
Leukopenia	8
Increased liver enzymes	5
Skin rash	5
Leg pain/bone pain/weakness/myalgias	5
Headaches	3
Fevers	3
Severe GI	2
Neutropenia	2
Hand/leg cramps	2
Leukocytosis	1
Thrombocytopenia	1
Photosensitivity	1
Tremors	1

The most encouraging observation in this study was that renal function in patients rescued continued to improve over the observation time. Steele (personal communication) has recently made the observation that RS-61443 prevents vasculopathy associated with allograft rejection. If these findings can be confirmed in human renal allografts, the decrease in arteriopathy would explain the continued improvement in creatinine levels. Clearly, one criticism of this pilot study is that one cannot be certain that in a number of patients, an additional course of high-dose steroids or OKT3/ALG would not have resulted in allograft rejection reversal. Therefore, a prospective randomized study was designed to address this question. This study is now in progress in several transplant centers in the United States, and will allow us to analyze the effect of RS-61443 in this setting with greater precision.

One of the most exciting aspects of this study as well as the previously mentioned experimental observations[7,8] is the ability of RS-61443 to reverse rejection. From a theoretical view, an antimetabolite should not be very effective once clonal proliferation has taken place and activated effector cells have been generated. Therefore, a second mechanism of action for RS-61443 has to be postulated. Allison and Eugui (personal communication) have recently suggested that RS-61443 downregulates expression of adhesion molecules. It was demonstrated that MPA-mediated depletion of guanosine triphosphate decreases the transfer of mannose and fucose to glycoproteins, some of which are adhesion molecules, facilitating the attachment of leukocytes to endothelial cells and to target cells. By this mechanism, MPA could decrease the recruitment of lymphocytes, monocytes, and neutrophils into sites of inflammation. Muller et al.[9] have shown that in activated human peripheral blood lymphocytes, treatment with MPA significantly decreases the transfer of mannose to dolycol phosphate and to membrane glycoprotein. If these findings can be extrapolated

to the *in vivo* situation, the observed reversal of allograft rejection with RS-61443 could be explained by the decreased recruitment of activated lymphocytes to the graft site.

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Discussion

Dr. G. Klintmalm (Dallas, Texas): Mr. President, members and guests: I am not really discussing the paper because I am one of the coauthors; I am here to give you a little update on where we stand with the drug in other organs. The same institutions have a multicenter study going for liver transplant rescue.

At this time we have enrolled 23 patients with acute unresponsive liver allograft rejection with the same definition and criteria for entry as in the kidney trial. The patients have had previous steroid therapy and OKT3 therapy without response. Of those, we have had 21 responses, 14 of those being complete responses and seven improved. Two failed, one of a chronic rejection and one of an acute rejection. One patient died of overimmunosuppression, a cytomegalovirus, and *Candida* infection. In the heart trial that is going on, involving a few other additional institutions, nine patients have been treated, and as you see, we have seen a response in all nine, complete or partial, and all nine patients are retaining the graft.

Of importance is also to say that the infectious complications have been few in the liver group; we have had eight patients with 14 infections. Of those 14, only four were of significant nature. And as far as side effects, they were the same as reported by Dr. Sollinger, very small indeed. For recipients of livers and hearts, we believe this drug is interesting. We believe the drug should be explored in further trials, which are planned to commence later this year.

Dr. Clyde F. Barker (Philadelphia, Pennsylvania): The search goes on for the ideal immunosuppressive agent. And I do not think we have it yet, but I believe that RS-61443 is one of the most promising and most exciting. The thoughtfulness with which Dr. Sollinger and his colleagues have approached the use of this and the logical sequence of their studies is to be commended. We know from his work and from the basic experimental work of others much more about the mechanism of action of RS and about the potential for its use than is the case in many of the new agents that have been brought forth with more publicity.

This paper addresses an additional factor that is very interesting, in transplantation biology, and Dr. Sollinger has already mentioned it. He has selected a stage in the sequence of post-transplant care at which rejection is the very difficult to deal with. Not only has clonal expansion occurred and the clinical symptoms of rejection manifested themselves, but in fact these have failed to respond to conventional therapy. For an immunosuppressive agent, this is the most rigorous test of all. The success of RS in this setting is what makes this work particularly exciting.

With most immunosuppressive agents, as Dr. Sollinger indicated, the optimal time to introduce them is at the time of the transplant, or, if possible, even before the transplant. Conversely, certain agents have had particular success when used at the time of rejection, for example, potent cytotoxic agents such as anti-lymphocyte serum and the monoclonal antibodies directed against lymphocytes. And RS looks as though it may share that capability with these agents. One wonders whether RS would be even more effective if used earlier in the course of a transplant.

The results are so good that one wonders, in fact, what the catch is to the use of this agent. All immunosuppressive agents have their limitations. Therapy was withheld in patients who had serious infection apparently because RS shares with all immunosuppressive agents risk in the face of infection. I wonder whether the agent is dangerous in the setting of viral infections.

Finally, I would like to know what the bottom line is in terms of the eventual outcome of the treatment of these patients. Because this was not a controlled series in which other forms of rescue therapy were employed instead of RS, would those patients in fact have simply had no other recourse or would there have been persistence with other forms of anti-rejection therapy? In other words, could some of these patients in the absence of the availability of RS have been rescued?

What was the bottom line in terms of the outcome of graft survival and patient survival overall at 1 year? In other words, do you know the outcome of the transplant in addition to the outcome of the rescue therapy?

Dr. David E. R. Sutherland (Minneapolis, Minnesota): Dr. Sollinger, what effect does RS-61443 have on rejection of other organs, such as the heart, in which chronic rejection is a very serious problem? Also, why is RS-61443 better than other drugs that inhibit purine synthesis? You alluded to an effect on adhesion molecules as one possible mechanism that allows an effect on clones that have already expanded. Are there drugs that are specific inhibitors or antagonists of adhesion molecules that do not affect purine synthesis? Their use would allow you to test the hypothesis, and such agents might even be superior to a drug that does affect purine synthesis.

With regard to the choice of patients to randomize, why wait until rejection is refractory? Why not randomize patients at the onset of rejection to standard therapy such as OKT-3 *versus* RS-61443, and then see find the incidence of refractory rejection. I also do not see any drawbacks to using RS-61443 as prophylaxis. You did a pilot trial using the drug prophylactically. Why not randomize?

Finally, Dr. Sollinger alluded to a possible effect on chronic rejection, and this is most intriguing. The patients he has treated had their rejection episodes at a time where chronic rejection is usually not the dominant lesion.

Why not administer the drug to patients with proven chronic rejection, such as patients who have a gradual elevation in creatinine a few years after the transplant, and in whom a biopsy shows histologic features typical of chronic rejection? Usually we do not treat this condition because it is inexorably progressive in spite of everything we have tried. It seems