Immunosuppressive medications for renal transplantation: A multiple choice question

Principal Discussant: Gabriel M. Danovitch
UCLA School of Medicine, Los Angeles, California, USA

CASE PRESENTATION
A 48-year-old black woman started hemodialysis six years ago after a 15-year history of systemic lupus erythematosus, for which she had received high doses of oral steroids and azathioprine. Six months after starting dialysis, she was referred to the UCLA renal transplant program. She was obese (BMI, 33 kg/m²) and had a long personal and family history of hypertension. Her family history also was notable for type-II diabetes; she had no potential living donors. An adenosine cardiotony cardiac perfusion study was normal. Her name was placed on the cadaveric transplant list.

In the four years that elapsed before she eventually received a cadaveric transplant, she was evaluated on an annual basis by the transplant program staff. Additionally, her blood was tested monthly to measure the level of panel-reactive antibodies against T-cells, which varied from 50% to 80% before absorption with dithiorthiol (DTT) and 20% to 40% after absorption. She was admitted to the hospital on 11 occasions for complications related to recurrent thrombosis of her vascular access. At the time of her transplant, she was being dialyzed via a graft in her left thigh, and she was receiving therapy with low-dose warfarin. Anticardiolipin antibodies were negative.

A cadaveric kidney became available for her two years ago. The kidney was from a 22-year-old victim of a gunshot wound and was mismatched at four human leukocyte antigen (HLA) loci. Donor-specific T-cell cytotoxic crossmatch was strongly positive, and the kidney was declined. The following month, she was admitted to the hospital with an episode of staphylococcal line sepsis, treated with a course of vancomycin.

Four months later, a zero-HLA-mismatched kidney was offered to her via the United Network for Organ Sharing (UNOS) six-antigen-match program. The donor, a resident of Maryland, was a 61-year-old victim of a cerebrovascular accident and had a five-year history of treated hypertension. The donor’s serum creatinine at the time of harvesting was 1.4 mg/dL after reaching a post-admission peak of 2.2 mg/dL. A renal biopsy performed at the time of harvesting showed 8 of 50 totally sclerosed glomeruli and “minimal” interstitial atrophy. Both standard T-cell cytotoxic and flow cytometry crossmatching were negative. Both the donor and recipient were positive for cytomegalovirus antibody. After a discussion with the patient and her nephrologist regarding the implications of accepting a kidney from a physiologically marginal donor, the transplant was carried out. The elapsed time from kidney harvesting to completion of the vascular anastomosis was 32 hours. Evaluation of the donor biopsy specimen after transplantation showed extensive nephroclerosis with moderate chronic parenchymal injury (Fig. 1).

Transplantation was technically uneventful. Urine output in the first 12 hours varied from 30 to 60 mL/hr despite a low-dose dopamine infusion, saline infusion, and high-dose intravenous furosemide. Immunosuppression was commenced with OKT3 in a dose of 5 mg in the operating room and daily for the following 10 days. Prednisone, 1000 mg, was given in the operating room and followed by 150 mg on the first day and tapered by 10 mg daily. A daily infusion of intravenous ganciclovir was given. On the first postoperative day, a transplant ultrasound with power Doppler showed no obstruction and good parenchymal flow; diastolic flow was reversed, and the resistive index was 1.1. Dialysis was required on the second day. The patient remained oliguric and was dialyzed every other day. On the seventh postoperative day, cyclosporine (Neoral), 4 mg/kg twice daily, and mycophenolate mofetil, 1500 mg twice daily, were started. Transplant biopsy, scheduled for postoperative day 10, was cancelled when her urine output began to increase steadily. The last dialysis was on the 10th postoperative day, and the patient was discharged from the hospital two days later. Her medications at the time of discharge are shown in Table 1, column 1.

The patient was followed in the renal transplant outpatient clinic every two to three days. Her renal function began to improve, and no further dialysis was required. By postoperative day 24, her serum creatinine had fallen to 3.8 mg/dL but then rose to 4.2 mg/dL. Renal ultrasound was unremarkable. A transplant biopsy showed findings consistent with healing acute tubular necrosis, tubulitis consistent with a Banff grade-II acute

Key words: acute rejection, tacrolimus, mycophenolate mofetil, basiliximab, daclizumab, sirolimus, CD25 receptor, cyclosporine.

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rejection, and vascular changes thought to be of donor origin. She received daily infusions of 5 mg/kg methylprednisolone for three days; her oral prednisone dose was rapidly tapered to 20 mg daily. Her serum creatinine fell to 2.2 mg/dL at six weeks post transplant. Her medications at that time are shown in Table 1, column 2.

Over the ensuing year, the patient was seen regularly at the transplant clinic. She felt good and returned to work. Her course was complicated by an episode of graft dysfunction ascribed to cyclosporine toxicity, a urinary tract infection with E. coli treated with ciprofloxacin, and a three-day hospital admission for an episode of bacterial pneumonia treated empirically with azithromycin. She gained an additional 8 kg in weight. Blood pressure was 130/90 mm Hg. Total serum cholesterol was 190 mg/dL with a low-density fraction of 120 mg/dL. At the end of the first post-transplant year, the serum creatinine fluctuated between 2.2 and 2.5 mg/dL, and a 24-hour urine collection contained 2.5 g of protein. A transplant biopsy showed evidence of chronic transplant glomerulopathy with patchy interstitial fibrosis and tubular atrophy. The patient's medications at that time are shown in Table 1, column 3.

### DISCUSSION

**Dr. Gabriel M. Danovitch (Medical Director, Kidney Transplant Program, Division of Nephrology, and Professor of Medicine, UCLA School of Medicine, Los Angeles, California, USA):** This patient illustrates many of the “multiple choice questions” faced by transplant programs as they attempt to take advantage of the expanding armamentarium of immunosuppressive medications at their disposal. Moreover, difficult choices commonly have to be made, as in this case, about whether to accept an organ, the functional quality of which was less than ideal. Should this particular kidney have been offered to her? On what basis was the decision made to choose her immunosuppressive protocol? How can we best protect her from the life-threatening complications that are a potential consequence of intensive immunosuppression? What can be done to maximize the functional life of her transplant after she had spent half a lifetime with end-stage renal disease? This Forum will attempt to answer these questions or, at the very least, provide a rational basis for addressing them.

To understand the design of the immunosuppressive protocol, one must not only be familiar with the medications per se, but also with the evolution of their introduction into clinical transplantation. In the 1960s and 1970s, utilization of corticosteroids, azathioprine, and the early polyclonal antilymphocytic agents was based largely on individual center experience without rigorous multicenter trials or predetermined end-points [1]. In the last two decades, all the new immunosuppressive agents have been introduced after clinical trials. The design of these trials and the end-points used to assess efficacy have had a major influence on the way in which the new agents are used. When the first clinical trials for cyclosporine were designed in the late 1970s and early 1980s, the primary end-
point used was “improvement of patient and graft survival,” which cyclosporine indeed achieved [2]. The results of renal transplantation were relatively poor at that time, so it was not hard to recognize the dramatic benefit of cyclosporine, which produced statistically significant improvement in patient survival and permitted graft survival rates of greater than 80% at one year. In Europe cyclosporine was often used alone, while in the United States it was usually combined with prednisone and azathioprine. Azathioprine was regarded as an adjunctive agent to cyclosporine and the combination was often called “triple therapy.” Although the benefits of cyclosporine were clear cut, its capacity to produce both acute and chronic nephrotoxicity was soon recognized to be a major “thorn in its side” [3]. In 1985, OKT3, the first monoclonal antibody in clinical medicine, was introduced into routine clinical care based on its capacity to successfully treat first acute rejection episodes [4]. But the toxicity of the drug tended to restrict its use to episodes of rejection that were resistant to high-dose steroids and, in some programs, to its use for the induction of immunosuppression as an alternative to polyclonal antibody preparations. With these medications—cyclosporine, azathioprine, corticosteroids, and the antibody preparations—the transplant community entered the 1990s achieving, with justifiable pride, success rates of up to 90% and minimal mortality in many centers. The number of available immunosuppressive medications was small, so relatively little variation existed among the protocols used in different programs.

Major developments occurred in the 1990s. Tacrolimus (FK506) was introduced into liver transplantation and eventually into renal transplantation as an alternative to cyclosporine because of its ability, proven in randomized clinical trials, to produce equivalent patient and graft survival [5]. Mycophenolate mofetil (MMF) was found to be a more effective adjunctive agent than azathioprine by virtue of its capacity to reduce the incidence of acute rejection episodes when used with cyclosporine [6], and later with tacrolimus [7], and corticosteroids. Two new humanized monoclonal antibodies, basiliximab and daclizumab, both targeted against the interleukin-2 (CD25) receptor, were approved for use in renal transplantation in 1998, again because of their ability to reduce the incidence of acute rejection episodes [8, 9]. Thymoglobulin, a polyclonal antibody available in Europe for several years, was approved for use in the US for the treatment of acute rejection [10]. In late 1999, sirolimus (rapamycin) was added to the immunosuppressive menu, again because when combined with cyclosporine and corticosteroids, it reduced the incidence of acute rejection episodes [11, 12]. Several new agents also are being evaluated in a similar fashion, that is, by their ability to reduce the incidence of acute rejection episodes. The ability of a new immunosuppressive agent to safely reduce the incidence of episodes of acute rejection thus has become the major yardstick by which new agents are assessed. It therefore behooves us to understand the implications and rationale for choosing this particular end-point.

Incidence of acute rejection episodes as an end-point for studies of new immunosuppressive drugs

The incidence of acute rejection episodes, typically “biopsy-proven,” has become the most frequently used marker of the effectiveness of new immunosuppressive drugs for the following reasons:

1. The excellent results of renal transplantation using currently available immunosuppressive agents, which yield a one-year graft survival of close to 90% and minimal mortality in most centers, make it extremely difficult to use patient or graft survival as markers to prove statistically significant benefit from the use of a new agent.

2. Acute rejection is a potent risk factor for the development of chronic allograft failure. In retrospective analyses, patients who have suffered episodes of acute rejection have a long-term graft survival of 20% to 45% less than patients who have not [13].

3. Acute rejection episodes are morbid events in themselves, requiring intensification of immunosuppression and sometimes hospital admission.

4. Most acute rejection episodes take place within the first few months of transplantation, and their presence can be proven by biopsy [14]. This pathophysiologic sequel permits rapid evaluation of the effectiveness of a new agent or protocol (a luxury not available when immunosuppressive drug trials are performed in other clinical circumstances, such as in systemic lupus erythematosus, rheumatoid arthritis, etc.).

As an example of this approach for evaluating the effectiveness of new immunosuppressive agents, Figure 2 contains data from one of the pivotal trials leading to the introduction of MMF [6]. This trial was a randomized, double-blind, placebo-controlled, multicenter, phase-III study to evaluate the efficacy of MMF in the prevention of acute rejection episodes during the first six months following renal transplantation. In this trial, standard therapy consisted of cyclosporine, prednisone, and azathioprine. The study compared two doses of MMF (1.0 g twice daily and 1.5 g twice daily) or azathioprine in combination with cyclosporine and prednisone. In the United States, the study involved 500 recipients of a first cadaveric transplant (very similar studies involving another 1000 patients were performed in Europe, Canada, and Australia). Figure 2A illustrates the clear-cut benefit of MMF with respect to the primary end-point: a statistically significant reduction in the incidence of acute rejection episodes, from nearly 50% in the azathioprine group to approximately 25% in both the MMF groups. The use of high-dose steroids and OKT3 also was markedly
reduced in the MMF groups. However, this study, which had a major impact on the way immunosuppression is practiced, did not demonstrate a statistically significant benefit of MMF with respect to patient or graft survival when estimated at either one or three years [15] (Fig. 2B).

Pivotal clinical trials led to the introduction of MMF, sirolimus, and the anti-CD25 monoclonal antibodies in clinical transplantation (Table 2). A statistically significant reduction in the incidence of acute rejection episodes within the first six post-transplant months was achieved for each of these drugs. However, on prospective analysis, neither patient nor graft survival was statistically significantly improved in any of these studies, either on short- or long-term follow-up.

As new immunosuppressive drugs and protocols are introduced and the incidence of acute rejection falls, it has become increasingly difficult to prove the statistically significant benefit of even newer agents. In the pivotal trials leading to the introduction of MMF, sirolimus, and the anti-CD25 monoclonal antibodies [6, 8, 9, 11], the incidence of acute rejection in the patients receiving the experimental drug protocol was compared to the incidence of acute rejection in patients receiving so-called “standard therapy” with cyclosporine and prednisone (typically combined with azathioprine in the US and placebo in Europe). The success of MMF in reducing the incidence of acute rejection led to it becoming part of an updated standard therapy protocol in many centers. In future trials of newer agents, MMF, or possibly sirolimus, will represent standard therapy, and statistical proof of further reduction in the incidence of acute rejection will likely be more difficult to achieve. Similarly, it is becoming more difficult to introduce new drugs based on their capacity to reverse episodes of acute rejection, as these episodes have become less frequent.

Although researchers have been unable to demonstrate statistically significant improvement in long-term graft survival in prospective analyses of the new generation of immunosuppressive agents, evidence emerging from large transplant registries indicates that the half-life of cadaveric kidneys is improving [16]. This discrepancy could reflect the lack of statistical power of the smaller prospective studies in proving the significance of small differences in graft survival. For example, if a new drug or protocol reduces the incidence of acute rejection episodes by 20%, and patients who suffer an episode of
which often have been developed in response to local experience. The components of a standard immunosuppressive protocol (Table 3) are relevant to all recipients, with the possible exception of two-haplotype-matched living related donors [21]. Since the risk of acute rejection is highest in the first weeks and months after transplantation (induction phase) and diminishes thereafter (maintenance phase), immunosuppression is at its highest level in this early period and is reduced for long-term therapy. The most feared side effects of immunosuppression—opportunistic infection and malignancy—tend to reflect the total amount of immunosuppression given rather than the dosage of a single drug. The availability of multiple potent immunosuppressive agents might tempt practitioners into a potentially dangerous polypharmacy. The benefit of the new agents in terms of their capacity to reduce the incidence of acute rejection episodes should be weighed against their cost, both economic and clinical. The total quantity of immunosuppression should be monitored and considered in all stages of the post-transplant course.

**Cyclosporine or tacrolimus?** One or the other of these two drugs currently comprises the backbone of transplant immunosuppression. Although much has been made of some distinct differences between cyclosporine and tacrolimus, the fact is that they are remarkably similar, and both are highly effective [22]. Both drugs exert their action by inhibiting the cytosolic phosphatase enzyme calcineurin, thereby preventing the passage through the nuclear membrane of activating factors for critical cytokine genes, particularly interleukin-2 [23]. The nephrotoxicity of both drugs has been well documented and cannot be differentiated pathologically. Transforming growth factor (TGF-β) might play a major role in their acute and chronic nephrotoxic effects and on their impact on the natural history of malignant tumors [24, 25]. Transplant registry data show no significant difference in long-term graft survival for patients taking cyclosporine or tacrolimus [26], so the choice between them is based largely on the profile of their side effects (Table 4). For example, tacrolimus is more toxic to pancreatic islets than is cyclosporine, and this effect is manifest clinically.

### Table 2. Incidence of biopsy-proven acute rejection episodes from selected randomized clinical trials using standard dose of experimental agent

<table>
<thead>
<tr>
<th>Agents compared</th>
<th>Control</th>
<th>Experimental</th>
<th>% Acute rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA, Aza</td>
<td>FK, Aza</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>CsA, Aza</td>
<td>CsA, MMF (2 g)</td>
<td>41</td>
<td>20</td>
</tr>
<tr>
<td>FK, Aza</td>
<td>FK, MMF (2 g)</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>CsA, Aza</td>
<td>CsA, basiliximab</td>
<td>48</td>
<td>33</td>
</tr>
<tr>
<td>CsA, Aza</td>
<td>CsA, daclizumab</td>
<td>43</td>
<td>27</td>
</tr>
<tr>
<td>CsA, Aza</td>
<td>CsA, rapa (2 mg)</td>
<td>24</td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviations are: CsA, cyclosporine; Aza, azathioprine; FK, tacrolimus; MMF, mycophenolate mofetil; rapa, sirolimus. All trials included standard dosage of corticosteroids. From Ref. 12.

### Table 3. Components of the immunosuppressive protocol

<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcineurin inhibitor</td>
<td>Cyclosporine, tacrolimus</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dose and regimen</td>
</tr>
<tr>
<td>Adjunctive agent</td>
<td>Azathioprine, MMF, sirolimus</td>
</tr>
<tr>
<td>Antibody induction</td>
<td>OKT3, ATGAM, thymoglobulin</td>
</tr>
<tr>
<td>Anti-CD25 monoclonal antibody</td>
<td>Basiliximab, daclizumab</td>
</tr>
<tr>
<td>Supplementary agents</td>
<td>CCB, HCR1</td>
</tr>
<tr>
<td>Infection prophylaxis</td>
<td>TMP-SMX, antivirals</td>
</tr>
</tbody>
</table>

Abbreviations are: MME, mycophenolate mofetil; CCB, calcium channel blocker; HCR1, HMG CoA reductase inhibitor; TMP-SMX, trimethoprim-sulfamethoxazole.

**General principles of immunosuppressive protocol design**

The variety of immunosuppressive drugs now available for use in clinical transplantation permit considerable permutations in immunosuppressive protocols. Transplant centers tend to be loyal to their own protocols,
particularly in African American patients [5]. Cyclosporine therefore might be the better choice in some centers where the population of African American patients is large because of the increased incidence of post-transplant glucose intolerance in patients who receive tacrolimus. Tacrolimus might be preferred in adolescent and other “cosmetically concerned” patients because of the more marked cosmetic changes associated with cyclosporine [21]. Cyclosporine might be more suitable in some patients because of the generally milder neurologic side effects [22]. Tacrolimus might be the preferred choice in recipients of simultaneous kidney and pancreas transplants because of its somewhat greater immunosuppressive potency despite its greater islet toxicity [27]. In the United States, approximately 70% of renal transplantation programs base their immunosuppression protocols on cyclosporine and the remainder on tacrolimus.

Which adjunctive agent? In this discussion I use the term “adjunctive agent” to describe the immunosuppressive drugs that are used, or were developed for use, in combination with a calcineurin inhibitor to enhance the potency of the immunosuppressive protocol, as measured by a decreased incidence of acute rejection episodes. Most programs in the United States use an adjunctive agent for prophylactic purposes starting from the immediate post-transplant period; some programs choose to introduce adjunctive therapy only in the event of an acute rejection episode. Azathioprine has been replaced by MMF (Table 2) [6]. Azathioprine and MMF are both antimetabolites and inhibit purine metabolism, but MMF does so in a more selective fashion through inhibition of the enzyme inosine monophosphate dehydrogenase [28].

Sirolimus became available for clinical use in late 1999. It is biochemically similar to tacrolimus and occupies the same receptor, but its mode of action is unique. It targets a protein, target-of-rapamycin (TOR), which plays a pivotal role in cell cycling, and does not inhibit calcineurin [29]. It is unclear at this time what extent transplant programs will prescribe sirolimus as a replacement for MMF. Both sirolimus and MMF were licensed based on their use in combination with cyclosporine and prednisone. Post-licensing studies have shown that MMF, tacrolimus, and prednisone comprise an effective combination [7]. It was originally believed that sirolimus and tacrolimus should not be used together, as they occupy the same receptor (FK-binding protein); preliminary studies suggest that this combination is acceptable and effective because the receptor is not fully occupied even when both are used [30]. Although sirolimus and MMF have not been compared directly, sirolimus is probably a more potent immunosuppressant and its side effect profile differs from that of MMF. In particular, sirolimus might have an unfavorable impact on the lipid profile, and MMF might produce troubling gastrointestinal side effects [6, 11]. Both drugs can suppress the production of formed blood elements to a degree comparable to azathioprine [21].

Antibody induction. A variety of antibody preparations are available for use in clinical transplantation, either for the treatment of acute rejection episodes or, in the early post-transplant phase, for the induction of immunosuppression (Table 5). Antibody induction therapy generally refers to the use of OKT3 or a polyclonal antibody (ATGAM or thymoglobulin) in the first 7 to 14 days after transplantation. The calcineurin inhibitor is withheld, or its dose is kept to a minimum until 2 to 3 days before the antibody course is completed. Induction protocols using OKT3 or a polyclonal antibody represent an alternative to the use of a calcineurin inhibitor in the early post-transplant period. When the anti-CD25 monoclonal antibody preparations are used, concomitant use of a calcineurin inhibitor is recommended [8, 9]. In so-called “sequential therapy,” OKT3 or the polyclonal antibody is administered and the calcineurin inhibitor is introduced only when renal function has fallen

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**Table 4. Comparative side effect profile of cyclosporine and tacrolimus**

<table>
<thead>
<tr>
<th>Drug interactions</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension and sodium retention</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pancreatic islet toxic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cosmetic side effects</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GI side effects</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cost</td>
<td>Similar</td>
<td>Similar</td>
</tr>
</tbody>
</table>

*Signs are: (+) known effect; (+ +) effect more pronounced; (−) no or little effect.*

*Summarized from [21, 22, 27, 35, 48].

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**Table 5. Antibody preparations for renal transplant immunosuppression**

<table>
<thead>
<tr>
<th>Indication</th>
<th>OKT3</th>
<th>Basiliximab</th>
<th>Daclizumab</th>
<th>Polyclonal</th>
<th>ATGAM</th>
<th>Thymoglobulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Rejection</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Symbols are: (+) approved indication; (+ +) unapproved but commonly used indication; + *, concomitant administration of calcineurin inhibitor recommended; (−), not indicated.*
to a specified level (for example, a plasma creatinine of 3 mg/dL). The antibody is discontinued as soon as adequate calcineurin inhibitor levels are achieved. A patient with a graft that functions well might receive only a few days of antibody treatment.

Evaluation of data from the large transplant registries has shown no long-term graft survival benefit of antibody induction in the majority of patients [31]. Patients at high immunologic risk, African American patients, children, and patients with delayed graft function might benefit from their use [32–34]. Antibody induction also might be indicated for patients requiring anticonvulsant drugs, which can make achieving therapeutic levels of calcineurin inhibitors difficult in the early post-transplant period [35]. Use of the polyclonal preparations obviates the first-dose side effects of OKT3; however, OKT3 is easier to administer [35] and is somewhat cheaper (~$600 per dose compared to $800 per dose for the polyclonals). The doses typically administered, thymoglobin is probably a more effective polyclonal agent than ATGAM [10] and evidence suggests that its administration immediately prior to transplantation reduces the incidence of delayed graft function, possibly by reducing the expression of adhesion molecules [36]. The use of OKT3 or the polyclonal antibodies is associated with a small but finite increase in the incidence of post-transplant malignancy and opportunistic infection; this risk is increased by the use of these drugs is prolonged or repeated [35–38].

The availability of MMF and the anti-CD25 monoclonal antibodies has reduced the use of OKT3 and the polyclonal antibodies at most centers. The two available anti-CD25 monoclonal antibodies, daclizumab and basiliximab, are very similar. From the therapeutic standpoint, they both have the capacity to reduce the incidence of acute rejection episodes by approximately 15% compared to placebo (Table 2), and they are both remarkably free of side effects [8, 9]. The approved dosage regimen for basiliximab (two doses of 20 mg at postoperative day 0 and 4) is more convenient than that for daclizumab (1 mg/kg on postoperative day 0 and at two-week intervals for a total of five doses); however, a shortened course of daclizumab appears also to be effective. In the absence of side effects, the decision to use these agents is based on each center’s assessment of their benefit, that is, the effectiveness in reducing the incidence of acute rejection, compared to their cost, approximately $1000 per dose. The anti-CD25 monoclonal antibodies are not indicated for the treatment of established acute rejection.

Supplementary agents. The inclusion of calcium-channel blockers, usually either diltiazem or verapamil, in the standard immunosuppressive regimen has several potential advantages. In addition to their antihypertensive properties, both drugs reduce calcineurin inhibitor-induced vasoconstriction and protect against ischemic graft injury and nephrotoxicity [39]. Both drugs compete with the calcineurin inhibitors for clearance by the P450 enzyme system, resulting in higher drug levels and permitting administration of a lower dose [40]. Calcium-channel blockers also might have some intrinsic immunomodulatory activity of their own that is related to the role of cytosolic calcium levels on gene activation [35]. The routine inclusion of calcium-channel blockers in the post-transplantation protocol has been reported to improve one-year graft survival by 5% to 10% [41].

The HMGCoA reductase inhibitors (HCRIs) have been shown to safely lower cholesterol levels and reduce the incidence of clinically severe rejection in cardiac transplant recipients [42]. A similar beneficial effect has been observed in a preliminary study in renal transplant recipients [43]. The mechanism of this effect might be related to the ability of HCRIs to suppress the cytokotoxic activity of natural killer cells [43]. Also, HCRIs might be important in the long-term post-transplantation regimen by virtue of their capacity to reduce the cardiovascular risk, the major source of morbidity and mortality after transplantation [44].

The prevention of infection remains a critically important part of modern immunosuppressive protocols [37]. A full review of this topic is beyond the scope of this discussion. The benefit of the new agents and protocols in terms of patient mortality and long-term graft survival is small, so any measurable increase in opportunistic infections and malignancy must be treated with great concern. The danger can be illustrated by two examples: the high incidence of Epstein-Barr virus–related lymphoproliferative disorders in pediatric recipients of liver transplants immunosuppressed with tacrolimus [45], and an outbreak of fatal Pneumocystis carinii infection in the phase-II trials of sirolimus at centers that were not using routine prophylaxis [46]. Ganciclovir and trimethoprim-sulfamethoxazole remain the “unsung heroes” of transplant immunosuppression.

Immunosuppressive drug avoidance and withdrawal

The availability of multiple effective immunosuppressive agents has stimulated attempts at minimizing or avoiding the most toxic components of the standard protocol. The most obvious targets for such efforts are corticosteroids and the calcineurin inhibitors.

Steroid withdrawal, the discontinuation of steroid administration post-transplantation, needs to be differentiated from steroid avoidance, in which steroids are administered only in the event of rejection. Steroid avoidance has never been popular in the United States, although it has been applied in Europe [47]. Steroid withdrawal is currently being re-evaluated in a multicenter trial in the US using a cyclosporine- and sirolimus-based protocol.

Steroid withdrawal is a tempting approach in selected patients, although the anxiety associated with withdrawal (both for the patients and their physicians!) has limited
its popularity. A randomized, blinded trial of steroid withdrawal at four months post-transplantation was performed in a group of patients with good graft function, who had not suffered rejection episodes, and who were receiving cyclosporine and MMF in standard doses (abstract; Matas et al, Transplantation 6:269, 1999). The trial was discontinued because of a 20% incidence of acute rejection in the group in whom the steroid was withdrawn, compared to a 5% incidence in the control group. Most of the rejection episodes occurred in African American patients. Steroid withdrawal thus should be considered only in patients who are at least several months post-transplant, have not suffered recent or recurrent rejections, and have excellent graft function [48, 49]. African American patients might not be suitable candidates for withdrawal and all patients should be warned of a small but finite increased incidence of rejection. A clear-cut benefit of withdrawal, in terms of certain steroid-related side effects (for example, bone disease, hyperlipidemia) has not been demonstrated, presumably because most of the familiar steroid-related problems are produced by the high doses used in the early post-transplant period [48]. Several studies have suggested that steroid-withdrawn patients might be subject to long-term deterioration in graft function, so enthusiastic reports of successful withdrawal should be evaluated with care [47–49].

In the pivotal trials leading to the introduction of cyclosporine, tacrolimus, MMF, and sirolimus, the drugs were continued over the long term, and the safety of their discontinuation was not studied in a rigorous fashion. It might be possible to withdraw these drugs in some stable patients [50] or to reduce their dose. Randomized trials are in progress to provide a definitive answer to the safety of this approach. Trials also are in progress using low doses that target lower blood levels of the calcineurin inhibitors in various combinations with MMF, sirolimus, and the anti-CD25 monoclonal antibodies. The potential advantage of these protocols is that they could maintain immunologic effectiveness while minimizing short- and long-term nephrotoxicity. Large multicenter European trials have evaluated protocols that do not use calcineurin inhibitors, replacing them with sirolimus or a combination of sirolimus and MMF [51, 52]. When sirolimus was used alone, graft survival (~90%) and the incidence of acute rejection (~50%) did not differ significantly between the patients who received a calcineurin inhibitor and those who did not [51]. Renal function was better in the calcineurin inhibitor-free group. Until the long-term results of these trials can be evaluated critically, one should carefully evaluate and review, together with the patient, the known risks and benefits of avoidance, withdrawal, or radical dose reduction of steroids and calcineurin inhibitors.

**Individualization of immunosuppressive protocols**

All patients are not equal with respect to the chances of rejection, graft loss, and development of drug-induced side effects, and protocols should take this into account. Patients who have received more than one transplant and patients with high levels of preformed antibodies can require more intense therapy [21, 35]. Young patients tend to be immunologically aggressive and might benefit from routine antibody induction [34]. Older patients have decreased tolerance for potent immunosuppression [53].

The role of race in the success of renal transplantation has been the subject of considerable debate and investigation. In the clinical trials leading to the introduction of tacrolimus, MMF, and sirolimus, African American patients have required higher doses of immunosuppressive drugs to achieve the same immunosuppressive benefit as did whites [5, 46, 54], and some programs routinely take this into account in protocol design [21, 33, 35]. As I said, African American patients are more likely to suffer acute rejection when steroids are withdrawn. In the US, allograft survival in African American recipients tends to be approximately 10% to 20% less than that for white recipients whether the transplant was from a living or cadaveric donor [19, 55]. Several factors have been proposed to explain the lower survival, including noncompliance and socioeconomic factors [55], the prevalence of hypertension in blacks [56], evidence of stronger immune responsiveness [57], and faster metabolism of immunosuppressive medications [58].

All donor kidneys are not equal with respect to their susceptibility to the immune or non-immune injury. Recipients of living related transplants, particularly from two-haplotype-matched donors, might require less immunosuppression [21, 35] and these kidneys are more likely to function well over the long term. On the contrary, kidneys that suffer delayed graft function are more susceptible to acute rejection and to chronic allograft failure [35, 59], particularly when mismatched for HLA [60]; the same is true for kidneys if early function improves only slowly [61]. Delayed graft function also has been shown to be a risk factor for long-term patient mortality [62]. A variety of factors related to the donor, the cause of the donor's death, and the circumstances of organ retrieval and transplantation predispose to ischemic injury, delayed graft function, and poorer long-term prognosis [35, 59].

**Should the kidney have been offered to this patient?**

The decision to transplant a kidney into this woman should be considered in the overall context of her end-stage renal disease and the difficult clinical dilemma resulting from her prolonged wait for a cadaveric kidney and her access failure. She had no potential living donors
because of the strong family history of renal disease and hypertension. Two years ago, she had a positive crossmatch to a poorly histocompatibility matched, but otherwise excellent, cadaveric kidney and was in dire need because of her access failure and preformed cytotoxic antibodies. The transplant team was then faced with a difficult and irrevocable decision—should they offer her the kidney that became available four months later? The kidney was a full histocompatibility match to her and the crossmatch was negative, but the organ had several features that predisposed it to delayed graft function. There were several donor-related problems, including advanced age, death by cerebrovascular accident, a history of hypertension, pre-harvesting acute renal dysfunction and a prolonged cold-ischemia time [16, 19, 20, 35, 59]. These features appear to outweigh the benefits of favorable histocompatibility matching [63, 64]. A history of hypertension is now obtained in approximately 25% of all donors in the US; both hypertension and death by cerebrovascular accident in the donor predispose to hypertension in the recipient [20, 65]. Hypertension is an important factor in determining racial differences in renal allograft survival [56].

The unfavorable histologic changes might have been underestimated in the original pathology report: 16% of the glomeruli were sclerosed, and interstitial and vascular changes were present. The increased use of physiologically marginal donor kidneys has led to an increased reliance on donor biopsies, taken at the time of organ retrieval, as a guide to the advisability of transplanting them, or even of transplanting both kidneys to a single recipient [66-69]. These biopsies are often performed outside of normal working hours, under intense time constraints, with less than ideal tissue fixation and staining. Under these circumstances, the percentage of sclerosed glomeruli has become a convenient marker of organ quality. Two groups have suggested that the determining feature should be the presence of 15% or 20% glomerulosclerosis [66, 67], and Remuzzi et al favor a scoring system that also includes interstitial and vascular changes [68]. A multivariate analysis, however, has shown that donor biopsy information adds little to what is already known from the donor’s age and circumstances of death [69].

Despite the unfavorable features of the kidney that became available, the significance of which were explained to her, the transplant team decided to offer her the kidney because she desperately needed it and because it was difficult to predict whether a more favorable, crossmatch-negative kidney would become available for her in the near future.

**Choice of immunosuppression and management of today’s patient**

Immunosuppression was commenced with antibody induction using OKT3. Antibody induction was used because her African American race, her preformed cytotoxic antibodies, the donor’s age and cause of death, and the prolonged cold ischemia time resulting from the organ’s transfer from the East Coast of the US to the West put her at increased risk of delayed graft function and early acute rejection [21, 32, 34, 59]. We chose OKT3 rather than ATGAM because of its greater ease of administration. Thymoglobulin was not available. The anti-CD25 monoclonal antibodies were not used since their documented clinical benefit has been in a low-risk population [8, 9]. Cyclosporine was chosen as her calcineurin inhibitor rather than tacrolimus, as she was deemed to be at particular risk of post-transplant diabetes mellitus because of her African American race, obesity, and family history of diabetes [5, 70]. We chose MMF as the adjunctive agent because it is more effective than azathioprine [15]; sirolimus was not available. The dose of MMF was 1500 mg twice daily rather than the standard 1000 mg twice daily because of evidence that African American patients require the higher dose to achieve the same degree of reduction of risk of rejection as do non-African American patients [15, 54]. She received a standard tapering dose of prednisone. We gave her ganciclovir intravenously and then orally as a form of “pre-emptive” therapy to prevent cytomegalovirus (CMV) infection. She was at high risk for CMV infection because we had administered OKT3 and because of evidence of prior donor and recipient CMV infection [36]. Bactrim (TMP-SMX) and nystatin were used as prophylaxis against oral candidiasis, urinary tract infection, and P. carinii pneumonia. Diltiazem was used as part of her anti hypertensive regimen and to permit a lower dose of cyclosporine [39, 40]. Its dose was fixed to avoid fluctuations in the cyclosporine level. Atorvastatin was used both for its effect on lipid levels and its potential immunologic benefit [42, 43].

Four weeks after receiving the transplant, the patient was treated with high-dose corticosteroids for what was probably a mild acute rejection episode in a background of resolving acute tubular necrosis and chronic histologic changes. High-dose “pulse” corticosteroids remain the first-line therapy for most episodes of mild rejection, and antibody preparations usually are held in reserve for recurrent episodes or first episodes that are severe, particularly if there is a component of vascular rejection [35]. The patient had received OKT3 for induction therapy; a second course of an antibody preparation within the first eight weeks after transplantation greatly increases the risk of lymphoproliferative disease and should be avoided if possible [38]. By three months after transplantation, her infection prophylaxis had been discontinued, and enalapril had been substituted for clonidine for blood pressure control. Angiotensin-converting-enzyme inhibitors and angiotensin II antagonists are safe and well tolerated in renal transplant patients [71]. Angiotensin II receptor blockade can decrease the levels of TGF-β that
have been implicated in the fibrogenesis that is a feature of chronic allograft nephropathy [72].

By one year after transplantation, she had evidence of chronic allograft failure. This term is now preferred to the previous, loosely used “chronic rejection” because of the contribution of both immune and non-immune factors to its pathogenesis [73]. Retrospective analyses have convincingly shown that the acute rejection episode that she suffered increased her risk of chronic allograft failure [13, 16]. The episode was made more likely by her delayed graft function, and it occurred despite an immunosuppressive regimen of proven effectiveness. The unfavorable donor factors that I mentioned conspired to further impair the long-term graft function through a process that has been likened to accelerated senescence [74].

The optimal management of chronic allograft failure remains unclear, and it has proven exceptionally difficult to design clinical trials that would define effective strategies [17]. Intensification of immunosuppression is generally not effective and is potentially dangerous; increasing the dose of the calcineurin inhibitor is likely to exacerbate its nephrotoxicity [35, 75]. Single-center studies have evaluated the strategy of adding MMF to the immunosuppressive regimen while reducing the dose of cyclosporine. The results have been mixed [75–77]. Replacement of the nephrotoxic calcineurin inhibitor with sirolimus is a tempting strategy that is yet to be tested systematically. Application of principles similar to those used for the management of chronic renal failure in native kidneys might be effective, and blood pressure control with ACE inhibitors or angiotensin II receptor blockers might slow the progression of allograft failure [71, 72]. Death of the patient accounts for more than 40% of all graft loss [44]. The most common cause of late post-transplant death is cardiovascular disease [20, 44]. Today’s patient has multiple risk factors for coronary artery disease and, in the absence of studies directly addressing these factors in the transplant population, it would seem appropriate to extrapolate from recommendations made to the general population. Therefore, we aggressively try to control her lipid levels and blood pressure while encouraging weight loss and regular exercise [20]. Attention to atherosclerotic risk factors could be the most important contribution to the improvement of the longevity of patients with successful renal transplants [44].

The management dilemmas that have faced this patient and her caregivers are by no means unique. Although the immunosuppressive choices that were made were successful in permitting her to navigate the first post-transplant year, the quality of the kidney that was transplanted might well come back to haunt her in the months and years ahead. No immunosuppressive regimen, no matter how effective, is likely to permit a physiologically marginal kidney to function as well as one from an “ideal” donor. As the waiting time for cadaveric organs inexorably lengthens, great care will be required to use the organs and drugs at our disposal wisely.

**QUESTIONS AND ANSWERS**

**Dr. Nicolaos E. Madias (Executive Academic Dean, Tufts University School of Medicine, Boston, Massachusetts):** Thank you, Dr. Danovitch, for a fine presentation. You reviewed the issue of individualization of patient protocols. Yet, as you indicated, most patients tend to be immunosuppressed in a very similar fashion. The result is that we likely are over-immunosuppressing many patients and are under-immunosuppressing others. Why have we not been more successful in this regard?

**Dr. Danovitch:** Indeed, the transplant field has been more successful in developing new immunosuppressive agents than in determining who should receive them. With the exception of fully HLA-matched sibling pairs, the available immunologic and histocompatibility markers have not proved to be adequately predictive for individual patients. So, for the moment, we are left with the rather broad demographic parameters that I outlined [21]. Hutchinson and colleagues reported that certain cytokine gene polymorphisms in transplant patients are associated with increased cytokine production and rejection risk [78]. Recognition of these polymorphisms eventually might permit more individualized therapy. Another way to approach immunosuppression is to start with a less aggressive protocol, such as by excluding corticosteroids or the adjunctive agent, and only intensifying immunosuppression in the event of an acute rejection. This approach is more popular in Europe than in the United States. Concern about the impact of acute rejection on long-term function has led to the trend of using intensive immunosuppression in the early post-transplant period. We are then left, as I said, with deciding which agents can be safely withdrawn and when. We obviously need more data.

**Dr. Madias:** Can available medications used in different combinations further improve the outcome of transplantation? Do you anticipate that a further reduction in the incidence of acute rejection will have a favorable impact on graft longevity?

**Dr. Danovitch:** Many transplant programs are achieving greater than 90% success, as measured by graft function at one year. There will inevitably be occasional graft loss due to technical or other complications. Therefore, we are approaching the maximization of short-term results. The current challenge lies in improving long-term success. A further reduction in the incidence of acute rejection might well be reflected in an improvement in long-term function, although I suspect that this improvement will be relatively small and difficult to measure. In our enthusiasm to reduce the incidence of early acute rejection episodes by using potent immunosuppressive
protocols, we must ensure that we do not engender morbid complications that will negate their benefit. Many of the so-called “antigen-independent” causes of long-term graft loss are related to the quality of donor organs and pre- and post-transplant recipient cardiovascular disease [20, 74].

**DR. ALAN WILKINSON (Division of Nephrology, UCLA Medical Center):** I suspect that some of the discrepancy that you describe between the measurable impact of acute rejection on long-term function in retrospective analyses compared to the lack of measurable impact on prospective analyses also might be due to the fact that not all rejections are equal. In clinical trials, most rejections are recognized early and treated quickly and therefore could have a lesser impact on long-term graft loss. Do you think that clinical trials accurately reflect routine clinical experience?

**DR. DANOVITCH:** That is a good point. Indeed, it is common for patients enrolled in clinical trials to do better than their non-trial counterparts even if they are in the control group, presumably because of the intensity of clinical monitoring and the early histologic confirmation and treatment of acute rejection. Fortunately, the clinical trials have had an impact on clinical management and the tendency now in most transplant programs is to biopsy the transplant to confirm a clinical impression of rejection rather than to treat a suspected rejection empirically [59].

**DR. MICHAEL BUNNAPRADIST (Division of Nephrology, Cedars Sinai/UCLA Medical Center):** What is your opinion of the role of the “protocol biopsy” in post-transplant immunosuppression management?

**DR. DANOVITCH:** Dr. David Rush and colleagues have pioneered the evaluation of the protocol biopsy in post-transplant management [79]. In doing so, they proposed the concept of “sub-clinical” acute rejection, which is defined by a usually mild lymphocytic infiltrate in the absence of an elevation in the serum creatinine level [55]. There is some question as to the pathologic significance of these infiltrates, but treating them as rejections might improve long-term graft function [79]. If this important observation can be confirmed, then the introduction of a protocol biopsy into routine care certainly would be a rational way to guide immunosuppressive management.

**DR. ARTHUR COHEN (Department of Pathology, Cedars Sinai/UCLA Medical Center):** A discussion of protocol biopsies should include consideration of a baseline biopsy at the time of transplantation. This approach permits identification of pre-transplant immunologic and non-immunologic damage and the more accurate interpretation of biopsies performed after transplantation. The baseline biopsy has to be performed by the surgeon correctly. It is not adequate to shave the immediate subcapsular zone of the kidney, which can be a very unrepresentative part of the kidney, especially in older donors who might have some degree of ischemia in the immediate subcapsular zone.

**DR. DANOVITCH:** At the behest of our nephropathy colleagues, several of the immunosuppressive trials referred to have included baseline and protocol biopsies; in patients in clinical trials, this is certainly appropriate. It is not yet clear to what extent the information obtained will affect routine clinical care. I am reluctant to recommend routine inclusion of additional procedures until we know more. I should add that in clinical trials it has sometimes proved difficult to persuade stable patients to undergo a protocol biopsy, and the degree of enthusiasm of the treating physicians for the procedure also has been variable. As a result, the statistical analysis of the biopsy data often has been incomplete [15].

**DR. COHEN:** Could you comment on the finding of polyoma viral infection in transplant patients? One recent report suggests that patients who receive tacrolimus are at much greater risk for developing this infection [80]. Does this risk enter into your consideration for selecting that drug versus cyclosporine? Why is polyoma viral infection of the transplant so rarely encountered?

**DR. DANOVITCH:** Human polyoma BK virus indeed has become a more frequently recognized infectious agent in immunosuppressed patients, but I suspect that it’s been there all along, but missed. It presents clinically in heavily immunosuppressed patients as a severe acute rejection that appears unresponsive to further intensification of immunosuppression, and the kidneys are usually lost [80]. It takes an astute pathologist like yourself to suspect its presence. The biopsy specimens show severe tubulointerstitial nephritis with large basophilic intranuclear inclusions. Special staining with polyoma virus monoclonal antibody confirms the diagnosis, and the viral DNA can be identified in plasma. Most of the cases have occurred in patients who have received tacrolimus, but the drug has typically been given for “rescue” after the use of antibody preparations and other agents. I doubt that the infection is specific for tacrolimus, and consideration of this risk does not influence the choice of agent. Rather, this virus is a reminder to us that we should always consider what our infectious disease colleagues call “the net state of immunosuppression” [37] and avoid excessive intensification of our regimens with the potent agents now available.

**DR. HARRY WARD (Division of Nephrology, King Drew/UCLA Medical Center):** Irrespective of how well we are doing with improved immunosuppressive protocols, we are still faced with a serious shortage of cadaveric organs. Considering the ratio of people awaiting organs to the availability of donors, do you think that we will have to ration cadaveric kidneys using some kind of broadly accepted criteria such as age, prior transplantation, or expected longevity? Should we direct the marginal kidneys to older patients or other high-risk groups?
Dr. Danovitch: The question you raised is an inescapable one, and the nephrology and transplant communities as well as the general public will need to come to grips with it in the years ahead. It will not be resolved until xenotransplants become a clinical reality. Personally, I am very reluctant to exclude, disadvantage, or promote certain patient groups with respect to access to transplantation, because all potential recipients can benefit from it either in terms of improved mortality rates or quality of life [44]. I don’t have any easy solutions. I do know that nobody wants to return to the kind of “thumbs-up, thumbs-down” decision-making that was a feature of the early days of hemodialysis.

Dr. Madias: Could you please comment on the available experience with dual grafting?

Dr. Danovitch: I will ask my surgical colleague to respond.

Dr. H. Albin Grisch (Department of Urology, UCLA Medical Center): By dual grafting I presume you are referring to the simultaneous use of both kidneys from older “marginal donors.” The use of both kidneys from pediatric donors transplanted “en bloc” is also a form of dual grafting. Both these maneuvers are a reflection of our attempts to maximally exploit the available cadaveric donor pool. Marginal kidneys are sometimes discarded for fear they will not provide adequate renal function for their recipients if they are used individually. Some centers now advocate the use of two kidneys from donors over the age of 60 if the renal function is impaired or if the biopsy taken at the time of organ retrieval reveals significant histologic damage [67]. One kidney can be placed in each iliac fossa using a preperitoneal midline incision or separate lower abdominal incisions. Alternatively, both kidneys can be placed on one side, with anastomosis of the vessels of one kidney to the common iliac artery and the vena cava. Early experience with transplantation of double marginal kidneys suggests that results of graft survival and renal function are comparable to those achieved with single kidneys from older donors [67, 68]. Older recipients might benefit more with kidneys from older donors, as their metabolic demands can be fewer. As yet, no nationally accepted guidelines exist for determining whether one or both kidneys should be transplanted; the decision has been made by individual transplant centers.

Dr. Gerald Friedman (Nephrologist, Upland, California): You discussed the problem of the shortage of cadaveric organs and the deteriorating quality of the cadaveric donor pool. What about the marginal recipient? I have patients in my practice who have been illicit drug users, patients who are noncompliant with therapy, and patients in their late sixties or older who end up on the transplant list and who receive kidneys before potentially better-suited recipients. Should we be more selective about the patients to whom we give organs?

Dr. Danovitch: In principle, all patients on chronic dialysis or with irreversible end-stage renal disease should be regarded as potential transplant recipients. When making decisions as to the appropriateness of transplant candidacy for individual patients, we should employ an evidence-based approach whenever possible and avoid making value judgments. Transplant programs and nephrologists need to educate patients about the relative risks and benefits of transplantation to help them make informed decisions. The American Society of Transplantation has published guidelines for the evaluation of transplant recipients. These guidelines will be updated on a regular basis and address in a detailed fashion the difficult issues to which you refer [81].

Dr. Robert Ettenberg (Department of Pediatrics, UCLA Medical Center): Would you comment on the contribution that noncompliance with medications might make to the evolution of chronic graft dysfunction?

Dr. Danovitch: You are certainly in order to bring up the issue of noncompliance in a discussion of the intricacies of transplant immunosuppression. In renal transplantation, clinically important noncompliance has been reported in 15% to 20% of recipients, and it substantially increases the risk of adverse immunologic events and even death [82]. Several social and demographic variables appear to affect the likelihood of noncompliance [83]. These include young age, psychiatric illness, low socioeconomic status, financial hardship, and a history of substance abuse. Noncompliance increases the risk of graft loss by three- to fivefold and is a common cause of late graft loss [82].

The approach to noncompliance by the transplant community needs to proceed both on a national and individual level. The financial strain on patients has been alleviated somewhat by the extension of Medicare coverage to 44 months, and the Institute of Medicine has recommended eliminating all time limits on Medicare coverage of immunosuppressant medications. As always, the development and maintenance of a trusting relationship between the patient and the caregiver is key to optimal outcome [82, 83].

Dr. David Lee (Division of Nephrology, Sepulveda Veterans Administration Hospital): You spoke of an increase in live kidney donation in the United States. Were the donors related or non-related? Please comment on the future, at least in the United States, of living non-related donation.

Dr. Danovitch: Most of the increase in living donation in the United States has come as a result of donation from people who are not biologically related. Non-related, or the term I prefer “emotionally related” donors, now account for approximately one-third of all living donations. A major stimulus for this expansion came as a result of the landmark report in 1995 by Terasaki and colleagues that the results of such donation approxi-
mated the results of donation from the more traditional biologically related sources [84]. Most of the biologically unrelated donors are spouses, close or distant relatives, close friends, or adopted family. Some programs accept donors who have no personal relationship with the recipient, so-called “good Samaritan” or altruistic donors. I feel strongly that our obligation to the health of donors relates not just to their physical health but also to their emotional well-being, and when the motive for the donation is not evident, it is very important that a careful psychiatric evaluation be included in the workup. In our transplant program, we have quite lively discussions on this issue. I tend to be conservative and feel more comfortable when I can identify a clear-cut emotional tie between the prospective donor and recipient. A recent Nephrology Forum by Dr. Susan Hou dealt with this issue in detail [85].

Dr. Alice Peng (Division of Nephrology, UCLA Medical Center): Rapamycin appears to be a potent but not nephrotoxic immunosuppressive agent. What do you think its role should be in future transplantation protocols?

Dr. Danovitch: Rapamycin was introduced into clinical transplantation after clinical trials in which it was used as an adjunctive agent to full-dose cyclosporine [11]. This combination might not be the most favorable one for exploiting the features of the drug, and I do not think that this is the way the drug will be generally used. In Europe, rapamycin has been used without a calcineurin inhibitor, and it appeared to be similar in its effectiveness to cyclosporine [51]. I am concerned that using both drugs in full doses will prove too toxic. Some preliminary results suggest that using rapamycin with low doses of tacrolimus or with mycophenolate mofetil is safe and effective [30, 52]. Rapamycin, together with tacrolimus and daclizumab, but in the absence of corticosteroids, has been used in the first consistently successful immunosuppression protocol for pancreas islet transplantation [86]. Clinical trials are in progress to critically evaluate these combinations.

In some tantalizing studies in small animal models, the tolerogenic effect of blockade of co-stimulatory molecules is increased by the induction of apoptosis in the responding T-cells. The calcineurin inhibitors impair this effect by blocking the induction of apoptotic signals, whereas rapamycin promotes apoptosis and improves graft tolerance [86]. These observations have important clinical implications because they eventually might permit an advance from the global immunosuppression produced by combinations of the agents currently at our disposal to a more selective immunosuppression produced by the apoptotic cell death of activated T-cells.

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Reprint requests to Dr. G. Danovitch, Kidney and Pancreas Transplant Programs, UCLA School of Medicine, 10833 Le Conte Avenue, Box 95176, Los Angeles, California 90095-1790, USA.

E-mail: gdanovitch@mednet.ucla.edu

REFERENCES


46. KAHAN BD, JULIAN BA, PESCOVITZ MD, et al: Sirolimus reduces the incidence of acute rejection episodes despite low cyclosporine doses in Caucasian recipients of mismatched primary renal allo-

47. STEGALL MD, WACHS M, EVerson GT, et al: Corticosteroid with-


50. KASISKE BL, HEIM-DETHOY K, MAJZ: Elective cyclosporine with-

51. GROTH CG, BÄCKMAN L, MORALES JM, et al: Sirolimus (rapamycin)-


53. MEIer-KRISches I, FRIEDMAN G, Jacobs M, et al: Infectious complica-


56. COSIO FG, DILLON JJ, FALKENHEIM ME, TESI RJ, et al: Racial differences in renal allograft survival: The role of systemic hyper-


59. DANOvITCH GM, NAST C: Diagnosis and therapy of graft dysfunction, in *Diagnosis and Transplantation*, edited by OWEN WF, PEREIRA BTG, SAVEGH MH, Philadelphia, Saunders, 2000, pp 568–583


62. TROPPMAN C, GILLINGHAM KJ, BENNETT E, et al: Delayed graft function, acute rejection and outcome after cadaver renal trans-


65. STRANGSAAD S, HANSEN U: Hypertension in renal allograft recipi-
ents may be conveyed by cadaveric kidneys from older donors with subarachnoid hemorrhage. *Br Med J* 292:1041–1044, 1986


69. POKORNA E, VITKO S, CHADIMOVA M, et al: Proportions of glomerulosclerosis in procurement wedge renal biopsy cannot alone dis-