Steroid-Resistant Kidney Transplant Rejection: Diagnosis and Treatment

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Abstract. Decreases in transplant function may be attributable to a variety of conditions, including prerenal and postrenal failure, cyclosporin A (CsA) toxicity, polyoma nephritis, recurrent glomerulonephritis, and rejection. The diagnosis of rejection should therefore be made on the basis of a transplant biopsy of adequate size, before the initiation of any therapy. Pulse steroid treatment (three to five 0.25- to 1.0-g pulses of methylprednisolone, administered intravenously) is the usual first-line therapy and has a 60 to 70% success rate, although orally administered prednisone (0.25 g) may be just as efficacious. Even if reverted, any rejection should trigger an at least temporary increase in basal immunosuppression, consisting of an increase in CsA or tacrolimus target levels, the addition of steroids or an increase in their dosage, the addition of mycophenolate mofetil, or a switch from CsA to tacrolimus. The addition of rapamycin or its RAD derivative may fulfill the same purpose. Steroid resistance should not be assumed before the fifth day of pulse steroid treatment, although histologic features of vascular rejection may indicate the need for more aggressive treatment earlier. Steroid-resistant rejection is traditionally treated with poly- or monoclonal antilymphocytic antibodies, with success rates of 60 to 70%. Their potential benefit must be carefully balanced against the risks of infection and lymphoma. More recently, mycophenolate mofetil has been successfully used to treat steroid-resistant rejection, but only of the interstitial (cellular) type. Switching from CsA to tacrolimus for treating recurrent or antibody-resistant rejection is successful in approximately 60% of cases. Plasmapheresis and intravenously administered Ig have been used in some desperate cases, with surprising success. Because none of the available drugs has a significantly better profile of therapeutic versus adverse effects, the possible benefits of continued rejection therapy must be continuously balanced with the potential for serious, sometimes fatal, side effects.

In the clinical practice of transplant nephrology, increases in serum creatinine of a certain magnitude (usually more than 20 to 30%) are sometimes treated as rejection without positive evidence obtained by transplant biopsy. However, if graft biopsies are consistently obtained before the “rejection” is treated with corticosteroids, diagnoses other than rejection are obtained surprisingly often (Table 1). Not uncommonly, normal tissue is obtained. Of course, this may represent a sampling error, which must be considered particularly in settings with a high likelihood of vascular rejection. If this possibility appears remote, however, and if postrenal failure is excluded on the basis of ultrasonographic findings, normal tissue in the presence of decreased graft function represents, by definition, prerenal failure. The most common cause is cyclosporin A (CsA)- or tacrolimus-associated renal vasoconstriction. A similar situation may be observed after the administration of thiazide diuretics, particularly together with an angiotensin-converting enzyme inhibitor (although evidence for hypovolemia may be scarce), or in younger patients, after vigorous exercise (presumably as a result of exercise-associated renal vasoconstriction and/or dehydration).

Another relevant and common finding is CsA- or tacrolimus-associated arteriolopathy, which requires careful consideration of the clinical context, because these lesions are known to persist for years after complete discontinuation of calcineurin inhibitors. Glomerular fibrin deposits may indicate a CsA- or tacrolimus-associated hemolytic uremic syndrome but may also be associated with vascular rejection.

It should be emphasized that therapeutic trials, performed either by administering steroids or by temporarily decreasing the CsA or tacrolimus dose, have no diagnostic value. Serum creatinine concentrations may decrease after pulse steroid administration although CsA toxicity is the problem. In addition, pulse steroid administration may mask the histologic signs of rejection in biopsies by diminishing the cellular infiltrate. CsA or tacrolimus dose reductions almost always decrease creatinine concentrations temporarily (by decreasing renal vasoconstriction), and they may do so even when rejection is ongoing.

Urinalysis has limited usefulness. Although grafts with proteinuria have poorer prognoses (1), proteinuria may be observed in cases of glomerulonephritis, transplant glomerulitis, or even CsA/tacrolimus-associated hemolytic uremic syndrome. Microhematuria, particularly with dysmorphic erythrocytes, may indicate recurrent glomerulonephritis, but the glomerulonephritis may not be the reason for the decrease in graft function. Most rejections present without microalbuminuria or
Table 1. Diagnoses other than rejection commonly obtained if suspected episodes of rejection are biopsied before treatment

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<th>Diagnosis</th>
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<tr>
<td>Normal tissue</td>
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<tr>
<td>CsA/tacrolimus-associated arteriolopathy</td>
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<tr>
<td>CsA/tacrolimus-induced hemolytic uremic syndrome</td>
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<tr>
<td>Polyoma nephritis</td>
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<td>Recurrent glomerulonephritis</td>
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* CsA, cyclosporin A.

microhematuria. Therefore, there is no substitute for a renal biopsy in cases of suspected or possible rejection.

Another entity that may masquerade as rejection is polyoma virus nephritis (2), which has increasingly been recognized in recent years in the context of newer and more potent immunosuppressants. To complicate matters, this destructive nephritis, which most commonly affects the distal nephron and for which no virostatic therapy exists, frequently arises in the context of recurrent rejection. If diagnosed, this complication presents clinicians with the dilemma that immunosuppression must be reduced because of the polyoma nephritis but must be maintained at a certain level because of previous severe rejections. Although no ready solution for this problem currently exists, it is believed that this nephritis is promoted by steroids. This complication highlights the absolute requirement for a graft biopsy before the treatment of presumed rejection.

**Assessment of Histologic Rejection**

If rejection is found in a transplant biopsy, recent evidence suggests that the overall rejection grade in the Banff 93 to 95 classification is much less important than the histologic type (3,4). Interstitial rejection (tubulitis) has a significantly better prognosis than vascular rejection (endothelialitis or intimal arteritis) (5), which mandates much more aggressive therapy in the latter. This distinction has therefore been introduced in the Banff 97 classification (6). Unfortunately, the diagnosis of vascular rejection is much more subject to sampling error. It is not unusual to be confronted with a fulminant creatinine increase whose histologic correlate may be, in the words of the pathologist, “a very discrete endothelialitis in one of two arteries contained in the biopsy.” Even discrete findings consistent with vascular rejection must therefore never be taken lightly but should be considered as evidence for vascular rejection.

To minimize sampling error, the graft biopsy should be of adequate size. The Banff 97 classification defines an adequate tissue sample as one that contains at least 10 glomeruli and two arteries (6). It has proven useful to collect two cores, which are immediately examined in 0.9% NaCl, under the microscope, to ensure that sufficient glomeruli are present. One of these cores is usually processed for light microscopy and the other for immunofluorescence (HLA-DR and C4d are useful markers that, when absent, are valuable for ruling out rejection) and, if desired, electron microscopy. The emphasis on vascular rejection also explains why fine-needle aspiration is vastly inferior to biopsy; the former can at best diagnose cellular rejection. In skilled hands, with an automated biopsy device and with a good ultrasound, the rate of severe complications is clearly <5%. The risk of nondiagnosis of vascular rejection (resulting in undertreatment) or of misdiagnosis of rejection (resulting in overtreatment) is much more significant.

**First-Line Treatment of Rejection**

When significant rejection is proven by biopsy, the usual first-line treatment is daily pulse steroid administration for 3 to 5 d. Doses in the range of 0.25 to 1.0 g of methylprednisolone (MP) are commonly used, and there are no data in the literature to suggest that the higher doses are more effective (7–10). Not even the question of whether intravenously administered MP is superior to orally administered prednisone (200 to 300 mg/d) has been decided in a prospective trial. Therefore, orally administered prednisone in this dose range probably is a reasonable alternative to intravenously administered MP. Of all rejections, 60 to 70% initially respond to this treatment; the others are considered steroid resistant.

Definitions of steroid resistance, however, vary widely, mainly in the time that one is willing to wait for the response and the number of MP pulses administered. As pointed out by Thiel et al. (11), there appears to be a trend toward shorter waiting times in studies designed to test new substances for their power to reverse rejection. The results of a questionnaire submitted to 17 transplant centers by Cantarovich and Soulillou (12) indicated that the mean period before considering a rejection as steroid resistant ranged from 3 to 7 d (median, 5 d). In our own recent study (13), we considered a rejection steroid resistant if creatinine levels did not return to within 20% of baseline within 3 to 5 d after the last MP pulse. A recent study by Shinn et al. (14) demonstrated that the creatinine courses of steroid-resistant and steroid-responsive cases separate no earlier than 5 d after the beginning of treatment. Therefore, 5 d appears to be the minimal time period for assessing the response to steroids.

The histologic features may also influence the waiting period. Because vascular rejection has a poorer prognosis (5), many centers quickly consider the use of antilymphocytic antibodies in such cases.

**Antilymphocyte Antibodies**

The use of antilymphocyte antibodies is the traditional means of treating steroid-resistant rejection, particularly of the vascular type. There are no data that conclusively demonstrate that the efficacy of any one of the polyclonal antilymphocyte globulins (ATG) (e.g., ATG-Merieux, ALG, ATGAM, and ATG-Fresenius) or the monoclonal antibody OKT3 is truly superior to that of another. These antibodies are, however, stronger immunosuppressants than steroids. In the first study of OKT3, which used it as a first-line treatment for rejection, 94% of all rejections were reversed, which was significantly more than the 75% reversed with steroid administration (15).

In steroid-resistant rejection, success rates with OKT3 have ranged between 50 and 96%, depending on the setting (16–19). It is still unclear whether basal immunosuppression should be
altered during OKT3 treatment, i.e., whether CsA administration should be temporarily discontinued, continued at a lower dose, or continued at the full dose. Clearly, the main problems in the use of OKT3 are its side effects, particularly the cytokine release syndrome and pulmonary edema, which make it mandatory to pretreat patients using diuretics and high-dose steroids.

Similar response rates have been reported for the various polyclonal ATG (13,20). In our own experience with ATG-Fresenius, this compound, with reversal rates of 63% (21) and 66% (13), has been superior even to OKT3. Although the degree of T lymphocyte suppression obtained with ATG-Fresenius is initially less than that obtained with OKT3, suppression lasts significantly longer. In fact, the CD4/CD8 ratio has been found to be depressed as much as 5 yr after treatment with ATG-Fresenius (22). Although thrombocytopenia may be a problem in the first days of ATG-Fresenius therapy, this polyclonal antibody is significantly better tolerated than OKT3 in all other respects; the same can probably be said for most ATG.

The undisputed efficacy of antilymphocytic antibody treatment is accompanied by the higher risk of infectious complications and lymphomas. This makes it mandatory to closely monitor patients for opportunistic infections and/or administer prophylactic treatments, which vary among centers (Table 2). Therefore, the use of antilymphocytic antibodies in the treatment of steroid-resistant rejection, particularly of the vascular type, requires judicious consideration of (1) the (remaining) crush type, (2) the propensity for infections, (3) the quality of the graft, (4) age, and (5) the overall situation of the patient, including his or her willingness to “fight” and his or her acceptance of a return to dialysis. Whether the newer anti-interleukin-2 receptor monoclonal antibodies (basiliximab and daclizumab) might be suitable for rejection therapy is unfortunately not known, because to date they have been used only for induction immunosuppression.

**Increase of Immunosuppression**

Rejection usually indicates that immunosuppression has been too weak. It is therefore reasonable to at least temporarily increase immunosuppression after a rejection episode. This may include the reintroduction of steroids (if steroid withdrawal triggered rejection), increases in CsA target levels (if the biopsy indicated no signs of arteriolopathy), or the addition of one of the newer immunosuppressants. Currently, the best documented of these newer immunosuppressants is mycophenolate mofetil (MMF) (25,26); however, rapamycin (27) and its derivative RAD are now reaching the market and most likely will also be valuable adjuncts. The recent finding that RAD, in contrast to CsA and tacrolimus (28), inhibits the growth of EBV-transformed B lymphocytes in vivo and in vitro (29) is certain to stimulate interest in the prevention of transplantation-associated lymphomas. Treatment with MMF (2 × 1.5 g/d) has been shown to be more effective than treatment with repeated MP pulses after steroid-resistant acute interstitial rejection (30).

**Change of Basal Immunosuppression from CsA to Tacrolimus**

Considerable data exist on the success of CsA-to-tacrolimus switching in the setting of rejection. In our own experience, changing to tacrolimus in cases of recurrent and/or refractory (even antibody-resistant) rejection is successful in a respectable 60% of cases (31). None of the studies reported in the literature was controlled, however, and tacrolimus has the newcomer’s advantage of being used when all other treatments have failed. Therefore, with tacrolimus being increasingly used as the primary calcineurin inhibitor, switching back to CsA may be equally well justified. Although tacrolimus appears to be slightly more potent than CsA (26), there may well be patients who are relatively resistant to tacrolimus and sensitive to CsA.

No advantage of using tacrolimus with respect to nephrotoxicity or infectious complications has thus far emerged, when compared with CsA.

**Nonstandard Treatments**

In severe cases of humorally mediated rejection, two treatment approaches have recently shown anecdotal success. Pascual et al. (32) reported the successful treatment of refractory humoral rejection with plasmapheresis and tacrolimus/MMF rescue. Jordan et al. (33) reported that the intravenous administration of immunoglobulin was able to reverse vascular rejection in a series of 10 patients with various transplants. Both of these treatments seem reasonable alternatives, which are, however, reserved for desperate cases. In theory, they could be combined, although this approach has not been attempted.

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**Table 2. Typical prophylactic treatments administered during a course of ATG**

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<thead>
<tr>
<th>Target</th>
<th>Patient Group</th>
<th>Agent</th>
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<tbody>
<tr>
<td>CMV</td>
<td>CMV-seropositive recipients or CMV-seropositive grafts</td>
<td>Gancyclovir, 10 mg/kg, intravenously 3 times/wk for 3 wk (dose adapted to renal function)</td>
</tr>
<tr>
<td>Fungi</td>
<td>All</td>
<td>Flucanazole, 50 mg/d</td>
</tr>
<tr>
<td><em>Pneumocystis</em></td>
<td>All</td>
<td>Cotrimoxazol, 960 mg, 3 times/wk</td>
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*a CMV, cytomegalovirus; ATG, antithymocyte globulins.*
Conclusion

The treatment of rejection has become more varied than the "give three MP pulses" paradigm of older times. Because numerous conditions can cause a deterioration of graft function, rejection should be diagnosed by biopsy only. Because rejection usually indicates insufficient immunosuppression, any rejection should prompt an increase of immunosuppression. Pulse steroid administration remains the first-line treatment for acute rejection and is efficacious in two-thirds of cases. Steroid-resistant rejections, particularly of the dangerous vascular type, are treated with various regimens, including administration of ATG, addition of MMF, and switching from CsA to tacrolimus. With the advent of new drugs, these second-line measures may soon change drastically. None of the currently available drugs has a significantly better therapeutic/adverse effect ratio, which makes it crucial for physicians to balance the possible benefits of continued rejection therapy with the increasing potential for serious, sometimes fatal, side effects. The patient's view of the situation and his or her individual perspective are key factors in the assessment.

References


