

Chapter 6: Treatment of Acute Rejection

- 6.1: We recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. (1C)**
- 6.2: We suggest treating subclinical and borderline acute rejection. (2D)**
- 6.3: We recommend corticosteroids for the initial treatment of acute cellular rejection. (1D)**
 - 6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. (2D)**
 - 6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids, and for recurrent acute cellular rejections. (2C)**
- 6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids (2C):**
 - plasma exchange;
 - intravenous immunoglobulin;
 - anti-CD20 antibody;
 - lymphocyte-depleting antibody.
- 6.5: For patients who have a rejection episode, we suggest adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate. (2D)**

OKT3, muromonab (anti-T-cell antibody).

Background

An acute rejection episode is the consequence of an immune response of the host to destroy the graft. It is of cellular (lymphocyte) and/or humoral (circulating antibody) origin. An acute rejection is clinically suspected in patients experiencing an increase in serum creatinine, after the exclusion of other causes of graft dysfunction (generally with biopsy). We know from the early days of transplantation, before there were effective antirejection treatments, that untreated acute rejection inevitably results in graft destruction. Therefore, it is strongly recommended that acute rejection episodes be treated, unless the treatment is expected to be life-threatening or to cause harm severe enough to preclude treatment.

Acute rejection is characterized by a decline in kidney function accompanied by well-established diagnostic features on kidney allograft biopsy. Subclinical acute rejection is defined by the presence of histological changes specific for acute rejection on screening or protocol biopsy, in the absence of clinical symptoms or signs. Acute cellular rejections are acute T-cell-mediated rejections and respond

to treatment with corticosteroids. Borderline acute rejection is defined by histopathological changes that are only 'suspicious for acute rejection' according to the Banff classification schema (99). A rejection episode is said to be unresponsive to treatment when graft function does not return to baseline after the last dose of treatment.

An antibody-mediated rejection is defined by histological changes caused by a circulating, anti-HLA, donor-specific antibody. The following criteria are generally used to determine whether an acute rejection is caused by a donor-specific antibody:

- i) staining of peritubular capillaries with C4d (fourth complement fraction);
- ii) the presence of a circulating, anti-HLA, donor-specific antibody and
- iii) histological changes consistent with an antibody-mediated rejection including (but not limited to) the presence of polymorphonuclear cells in peritubular capillaries.

Rationale

- Several causes of decreased kidney function can only be distinguished from acute rejection by biopsy.
- Treatment of decreased kidney allograft function that is not caused by acute rejection with additional immunosuppressive medication may be harmful.
- Treating subclinical acute rejection discovered on protocol biopsy may improve graft survival.
- Most acute cellular rejection responds to treatment with corticosteroids.
- Treating acute cellular rejection that is unresponsive to corticosteroids or recurs with an anti-T-cell antibody may prolong graft survival.
- Increasing the amount of immunosuppressive medication after an acute cellular rejection may help prevent further rejection.
- Treating borderline rejection may prolong graft survival.
- A number of measures may be effective in treating antibody-mediated rejections, including plasma exchange, intravenous immunoglobulin, anti-CD20 antibody and anti-T-cell antibodies.

Although there are no RCTs to establish that obtaining a biopsy improves outcomes of suspected acute rejection, there are alternative diagnoses that might mimic an acute rejection episode. BK polyomavirus (BKV) nephropathy would generally be treated differently than acute

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rejection, for example with a reduction in immunosuppressive medication. Therefore, logic dictates that, whenever possible, biopsy confirmation should be obtained to avoid inappropriate treatment.

Some centers use protocol biopsies to detect and treat subclinical acute rejection. In a RCT, the detection and treatment of subclinical acute rejection in patients ($N = 72$) on CsA, MMF and corticosteroids resulted in better graft function (100,101). However, in a larger ($N = 218$) multicenter RCT in patients on tacrolimus, MMF and corticosteroids, protocol biopsies and treatment of subclinical acute rejection were not beneficial (102). Finally, in a single-center RCT of 102 recipients of living-donor kidneys (treated with CsA [$N = 96$] or tacrolimus [$N = 6$], MMF [$N = 55$] or azathioprine [$N = 47$] and corticosteroids) protocol biopsies and treatment of subclinical acute rejection resulted in improved graft function (103). Uncontrolled data suggest that, when the incidence of clinical acute rejection is low, the number of patients with subclinical acute rejection may be too small to warrant the inconvenience and cost of protocol biopsies (104).

Corticosteroid therapy is the most commonly used, first-line treatment for acute cellular rejection episodes. Although most patients respond to corticosteroids, the dose and duration of treatment has not been well defined by RCTs. Treatment starting with intravenous solumedrol 250–500 mg daily for 3 days is a common practice.

Treatment of acute cellular rejection with an anti-T-cell antibody (muromonab [OKT3], ATG or ALG) is more effective in restoring kidney function and preventing graft loss than treatment with corticosteroids (105). The systematic review concluded that treatment with an antibody is associated with more adverse effects, but whether the overall benefits of antibody treatment vs. corticosteroids outweigh harm is uncertain (105). There are no RCTs examining whether anti-T-cell antibodies vs. corticosteroids should be the initial treatment of Banff IIA or IIB (vascular) rejection. A low strength of evidence suggests no net benefits or harm between antibodies or steroids alone (see Evidence Profile in Supporting Table 39 at <http://www3.interscience.wiley.com/journal/118499698/toc>).

Studies suggest that steroid-resistant or recurrent T-cell-mediated rejection responds to treatment with polyclonal or monoclonal anti-T-cell antibodies (105). It is also possible that the addition of MMF to the postrejection maintenance immunosuppressive medication regimen, or replacement of azathioprine with MMF, will help to prevent subsequent acute rejection. A RCT ($N = 221$) compared MMF to azathioprine in the treatment of first acute rejection (106). Patients receiving MMF had fewer subsequent rejections, and among the 130 who completed the trial, at 3 years graft survival was better in the MMF group (106). A summary of

the RCTs on replacement of azathioprine by MMF in the setting of rejection is provided in Supporting Tables 40–41.

Whether or not to treat borderline acute rejection is controversial. There are no RCTs addressing whether treatment of borderline acute rejection prolongs graft survival, and whether overall benefits outweigh harm.

If function does not return to baseline, or if there is a new decline in function after successful treatment of an acute rejection, a biopsy should be considered to rule out additional rejection, BKV nephropathy and other causes of graft dysfunction.

Anti-T-cell antibodies (OKT3, ATG, ALG) can be used when corticosteroids have failed to reverse rejection or for treatment of a recurrent rejection. In such circumstances, benefits generally outweigh harm. However, there is inadequate evidence from RCTs to conclusively establish the best treatment for steroid-resistant or recurrent acute cellular rejection (see Evidence Profile in Supporting Table 38). Most studies comparing OKT3 to ATG or ALG did not have adequate statistical power to show a difference in efficacy. However, in one RCT, ATG was better tolerated than OKT3 (107). When a steroid-resistant rejection or a recurrent rejection does not respond to a lymphocyte-depleting antibody or OKT3, a new biopsy should be considered to rule out alternative causes of graft dysfunction.

Therapeutic strategies that include combinations of plasma exchange to remove donor-specific antibody, and/or intravenous immunoglobulins and anti-CD20⁺ monoclonal antibody (rituximab) to suppress donor-specific antibody production have been used to successfully treat acute humoral rejection. However, the optimal protocol to treat acute humoral rejection remains to be determined. Indeed, there are no RCTs with adequate statistical power to compare the safety and efficacy of these different therapeutic strategies. In a RCT in 20 children, rituximab was associated with better function and improved postrejection biopsy scores compared to treatment with anti-T-cell antibody and/or corticosteroids (108). Clearly, additional studies to define the optimal treatment of acute humoral rejection are needed.

Research Recommendations

Additional RCTs are needed to determine:

- whether treating borderline acute rejection improves outcomes;
- when protocol biopsies and treatment of subclinical acute rejection are cost-effective;
- the optimal treatment for antibody-mediated acute rejection.