Evaluation and Treatment of Acute Rejection in Kidney Allografts

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Abstract
Advances in immunosuppressive therapy have drastically improved acute rejection rates in kidney transplant recipients over the past five decades. Nevertheless, it should remain high on any differential diagnosis of unexplained graft dysfunction because of the potential negative effect on graft longevity. Understanding the pre- and post-transplant risk factors for acute rejection can help estimate the probability of immunologic graft damage, and accurate identification of the type and severity of acute rejection will guide appropriate treatment. Tissue biopsy remains the gold standard for evaluating immunologic graft damage, and the histologic definition of acute rejection has evolved in recent years. Intravenous steroids and T cell depletion remain the standard therapy for T cell–mediated rejection and are effective in reversing most cases. Plasma exchange and intravenous Ig, with or without rituximab, are most commonly used for the treatment of antibody-mediated rejection and several newer agents have recently been investigated for severe cases. This review aims to provide the general nephrologist caring for transplant recipients with an approach to immunologic risk assessment and a summary of recent advances in the diagnosis and treatment of acute graft rejection.


Introduction
Transplantation of donor organs to non-HLA identical recipients introduces a stimulus for alloimmune responses, clinically referred to as graft rejection. Fifty years of research and development continues to elucidate the mechanisms underlying these responses, and has led to an evolution of immunosuppressive agents targeting these mechanisms. Over time these agents have become increasingly effective at inhibiting the transplant recipient’s immune response. As a result, acute rejection rates have steadily declined from nearly 100% in the first era of organ transplantation to approximately 10% more recently (1,2) (Figure 1). Not surprisingly this precipitous fall in acute rejection incidence has been mirrored by dramatic improvements in 1-year graft survival, especially after the introduction of cyclosporine in the mid-1980s and T cell–depleting induction in the mid-1990s (3). Nevertheless acute rejection, when it occurs, has the potential to significantly affect graft survival (4,5) and should remain high on the differential diagnosis for unexplained graft dysfunction in a transplant recipient.

As our understanding of the alloimmune response has evolved, so has the classification of clinical acute rejection episodes. Initially characterized as “steroid responsive” and “steroid nonresponsive,” acute rejection is now broadly characterized as either “T cell mediated” or “antibody mediated,” respectively (6). These two forms of acute rejection result from separate mechanistic pathways, are associated with unique histologic findings and prognoses, and require distinct approaches to treatment. This review will summarize a modern approach to risk assessment, diagnosis, and treatment of acute rejection.

Acute Rejection Risk
An individual’s immunologic risk at the time of transplant has conventionally been attributed to factors such as overall level of anti-HLA sensitization (panel reactive antibody), repeat transplant, black race, and recipient age. Wehmeier et al. (7) recently examined traditional risk factors in 527 kidney recipients, showing pretransplant donor-specific antibodies (DSA) and HLA A/B/DR mismatch to be the main predictors of antibody-mediated rejection and T cell–mediated rejection, respectively, whereas panel reactive antibody and repeat transplantation had no predictive effect. With this in mind, it is worth noting the degree of immunologic risk conferred by pretransplant DSA will depend on characteristics of the antibodies detected. Approximately 30%–50% of patients with pretransplant DSA at titers strong enough to warrant desensitization before transplant will experience acute antibody-mediated rejection (8), whereas lower-level antibodies do not appear to increase acute rejection risk or graft survival in the intermediate term (9).

In the post-transplant period, acute rejection risk is largely determined by immunosuppression regimen and exposure. Currently in the United States, 75% of kidney recipients receive rabbit antithymocyte globulin (rATG) induction and >90% receive maintenance immunosuppression consisting of tacrolimus and mycophenolate mofetil, with or
without prednisone, as these regimens have historically been associated with lower rates of acute rejection (10). Strategies to reduce calcineurin inhibitor (CNI) exposure using mammalian target of rapamycin inhibitors (mTOR’s) have generally been met with higher rates of acute rejection and side effects (11). Calcineurin inhibitor-free maintenance immunosuppression with the newer agent belatacept has resulted in favorable, longer-term outcomes but with higher rates of T cell–mediated rejection (12); however, post hoc analysis has shown a significant reduction in DSA development in those receiving belatacept versus cyclosporine (1%–4% versus 12%, respectively) (13). Adams et al. (14) recently published their center’s early experience showing significant reduction in acute rejection in patients treated with belatacept by adding tacrolimus to the existing belatacept regimen followed by a steady taper over the first post-transplant year (acute rejection rates of 51% with belatacept alone versus 16% with belatacept plus tacrolimus taper).

Despite the prevalence of tacrolimus use for the prevention of acute rejection in transplant recipients, firm recommendations for appropriate dosing and exposure to prevent acute rejection have not been established. Recent data from our group and others have shown correlations with overall tacrolimus exposure and acute rejection risk (15–17). In a cohort of 538 consecutive transplant recipients initiated on tacrolimus-based triple immunosuppression at the University of Colorado, mean tacrolimus levels <8 ng/ml throughout the first year increased the risk of DSA development (odds ratio, 2.5 (95% CI 1.32–4.79); P<0.005 versus >8) and levels of 4–6 versus >8 ng/ml were associated with a 2.3-fold higher risk of acute rejection (16).

Thus, when considering the differential diagnosis of graft dysfunction, assessment of overall immunologic risk can help estimate acute rejection probability. A high index of suspicion, for example, would be warranted in a young patient with lower tacrolimus trough levels during the first post-transplant year and/or suspected immunosuppression non-adherence. Alternatively, non-immunologic causes may first be considered in an older patient who received rATG induction with consistently therapeutic tacrolimus levels.

**Acute Rejection Diagnosis**

The gold standard for diagnosing acute rejection in kidney transplant recipients is tissue biopsy. Indications to pursue graft biopsy over concern for acute rejection include either an acute, otherwise unexplained deterioration in graft function or the presence of a biomarker consistent with acute rejection. As described in the preceding section, assessment of a patient’s immunologic risk at the time of and after transplant can help further define pretest probability of acute rejection when contemplating the utility of biopsy; however, allograft biopsy is generally considered a safe procedure and should be pursued without delay in patients with graft dysfunction that is not explained by other nonimmunologic causes. Allograft histology is interpreted using the Banff classification of kidney allograft pathology, which has undergone extensive updating and revision since its development in the 1990s (6) (Table 1). The diagnostic criteria for T cell–mediated rejection have undergone little change in recent years, and include lymphocytic infiltrate of tubules (tubulitis) and larger vessels (vasculitis), with the severity of these lesions depending on the degree of lymphocytic infiltrate per high-powered field (Figure 2, A–C).

In contrast, the Banff classification of acute antibody-mediated rejection continues to evolve with the ongoing recognition of its variable histologic presentation. Antibody-mediated rejection was first recognized within the Banff classification in the early and mid-2000s and required three features for diagnosis: (1) active tissue injury, (2) immunohistologic evidence of peritubular capillary complement split-product C4d deposition, and (3) circulating DSA. This relatively strict definition resulted in a problematic underdiagnosis of antibody-mediated rejection.

**Figure 1.** Decline of 1-year incidence of acute rejection over time with approximate date of immunosuppression medication introduction. Acute rejection rates have steadily declined over time with the introduction of increasingly effective immunosuppression. Modified and updated from Zand (3).
rejection; especially concerning given the long-term clinical implications of antibody-mediated graft damage (18). Subsequent revisions have allowed for exceptions to these initial criteria, the most significant occurring in 2013 after several studies suggested an antibody-mediated rejection phenotype that lacks detectable C4d staining (19–21).

Microarray analysis of endothelial transcripts, work that has been largely pioneered by Halloran et al. (22), provides further evidence for C4d-negative antibody-mediated rejection. This technique applies a molecular phenotype to allograft tissue using extracted RNA to examine patterns of altered gene expression. Sis et al. (21) examined 173 for-cause biopsy specimens and showed poor prognosis in samples with DSA and endothelial transcript expression consistent with antibody-mediated rejection, only 40% of which showed C4d positivity. As a result of these studies and others, the revised 2013 Banff criteria for antibody-mediated rejection diagnosis removed the requirement for C4d detection and broadened this category to include “evidence of current/recent antibody interaction with vascular endothelium,” which may include either (1) positive C4d staining, (2) at least moderate microvascular inflammation, or (3) increased expression of endothelial gene transcripts (20).

The most recent Banff consensus notes studies showing a lack of DSA in patients with biopsy specimens

Table 1. Histologic criteria for diagnosing acute allograft rejection according to Banff 2017 guidelines (6)

<table>
<thead>
<tr>
<th>Acute T cell–mediated rejection (TCR)</th>
<th>Acute antibody-mediated rejection (AMR): all three criteria below required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia  &gt;25% Interstitial inflammation with moderate tubulitis (t2)</td>
<td>Histologic evidence of tissue injury including one or more of the following:</td>
</tr>
<tr>
<td>Ib  &gt;25% Interstitial inflammation with severe tubulitis (t3)</td>
<td>Microvascular inflammation (g&gt;0 and/or ptc&gt;0)</td>
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<tr>
<td>IIa Mild-to-moderate intimal arteritis (v1)</td>
<td>Arteritis (v&gt;0)</td>
</tr>
<tr>
<td>IIb Severe intimal arteritis (v2)</td>
<td>Thrombotic microangiopathy</td>
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<tr>
<td>III Transmural arteritis and/or fibrinoid necrosis</td>
<td>Acute tubular injury</td>
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<td></td>
<td>Evidence of current/recent antibody interaction with endothelium including one or more of the following:</td>
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<td></td>
<td>Positive C4d staining of peritubular capillaries</td>
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<td></td>
<td>Increased expression of gene transcripts in biopsy tissue strongly associated with AMR</td>
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<tr>
<td></td>
<td>Serologic evidence of donor-specific antibodies (DSA)</td>
</tr>
<tr>
<td></td>
<td>Positive C4d staining or presence of AMR-associated gene transcripts may substitute for DSA</td>
</tr>
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| t, tubulitis; v, arteritis; g, glomerulitis; ptc, peritubular capillaritis. |

Figure 2. | Histologic presentation of acute rejection. (A) Banff grade 1a with moderate lymphocytic infiltration of the tubules (arrows). (B) Banff grade 1b with severe lymphocytic interstitial infiltration and tubulitis (arrows). (C) Banff grade 2a with arterial intimal lymphocytic infiltration (arrows). (D) Peritubular lymphocytic infiltration characteristic of antibody-mediated rejection (arrows). (E) Positive C4d staining of the peritubular capillaries by immunohistochemistry.
demonstrating significant microvascular inflammation as well as a low false positive rate of C4d staining, and has now removed the requirement for documented circulating DSA in the setting of positive C4d staining and microvascular inflammation (6) (Figure 2, D and E, Table 1).

Although assessment of allograft tissue remains the gold standard for diagnosing acute rejection, tissue biopsy is resource intensive, presents a potential risk to patients, and has been associated with significant sampling error and variability in pathologic interpretation. Numerous studies of urine and blood biomarkers, such as CXCL9, CXCL10, granzyme B, perforin, and Fas ligand, have generally shown mixed sensitivity and specificity for identifying acute rejection, differentiating T cell–mediated rejection from antibody-mediated rejection, and distinguishing immunologic injury from other forms of graft damage (reviewed by Naesens and Anglicheau [23]). Short non-coding single-stranded microRNA have improved stability in urine compared with mRNA (24) and decreased urinary miR-210 levels have been associated with T cell–mediated rejection and subsequent 1-year GFR decline (25). Recently, donor-derived cell-free DNA (cf-DNA) profiling has been applied to the noninvasive diagnosis of antibody-mediated rejection, with results from the multicenter “Circulating Donor-Derived Cell-Free DNA in Blood for Diagnosing Active Rejection in Kidney Transplant Recipients” (DART) study leading to a Medicare-reimbursable status in 2017. This study associated cf-DNA levels with 242 biopsy specimens (204 clinically indicated) and showed a negative predictive value for antibody-mediated rejection of 69% with a negative predictive value of 100%, but did not discriminate between those with and without T cell–mediated rejection.

Thus, despite its downsides, tissue biopsy remains the gold standard for diagnosing acute rejection in transplant recipients and noninvasive biomarkers have failed to completely remove tissue diagnosis due in part to inconsistent performance between studies. However, normal results from assays with high negative predictive value, such as donor-derived cf-DNA, may offer a level of reassurance to providers and patients with abnormal clinical findings (DSA, graft dysfunction) in whom tissue biopsy is either not feasible or considered too high risk.

**Acute Rejection Treatment**

The approach to treatment of the transplant recipient with acute rejection relies on accurate diagnosis and classification of the immunologic pathology. Treatment strategies differ between T cell–mediated rejection and antibody-mediated rejection, and aggressiveness of treatment generally follows severity of lesions that are diagnosed. Graft prognosis after treated acute rejection also depends on type and severity (4); however, any untreated clinical acute rejection episode will ultimately result in accelerated graft loss. Thus timely recognition and diagnosis of acute rejection is crucial to promptly initiate appropriate treatment. Treatment options for acute rejection are listed in Table 2, and a

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Methylprednisolone</td>
<td>TCR: Banff Ia, Ib</td>
<td>Multiple, anti-inflammatory</td>
<td>Hyperglycemia, hypertension, other metabolic effects</td>
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<td>glucocorticoid</td>
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<td>rATG</td>
<td>TCR: Banff Ia, Ib</td>
<td>T cell depletion</td>
<td>Fever, chills, hypertension, hypotension, leukopenia, infusion reaction, serum sickness</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>AMR</td>
<td>Antibody removal</td>
<td>Fever^a^, chills^a^, urticaria^a^, TRALI^a^, bleeding</td>
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<tr>
<td>IVIG</td>
<td>AMR</td>
<td>Multiple “immunomodulatory”</td>
<td>Infusion reaction including headache, fever, chills, urticaria, back pain, abdominal pain, nausea, vomiting</td>
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<td>effects including antibody</td>
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<td>clearance, neutralization, and</td>
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<td></td>
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<td>inhibited production, Fc</td>
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<td>receptor saturation, complement</td>
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<td></td>
<td></td>
<td>inhibition</td>
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<tr>
<td>Rituximab</td>
<td>AMR</td>
<td>Anti-CD20 B cell depletion</td>
<td>Infusion reaction, HBV reactivation, PML</td>
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<td>Bortezomib</td>
<td>AMR</td>
<td>Plasma cell apoptosis via</td>
<td>Peripheral neuropathy, fatigue, generalized weakness</td>
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<td>proteasome inhibition</td>
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<tr>
<td>Eculizumab</td>
<td>AMR</td>
<td>Terminal complement C5</td>
<td>Meningococcal infection, influenza, peritonitis</td>
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<tr>
<td>C1-INH</td>
<td>AMR</td>
<td>Classic complement pathway</td>
<td>Headache</td>
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<td></td>
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<td>inhibition</td>
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TCR, T cell–mediated rejection; rATG, rabbit anti-thymocyte globulin; AMR, antibody-mediated rejection; TRALI, transfusion-related acute lung injury; IVIG, intravenous immunoglobulin; HBV, hepatitis B virus; PML, progressive multifocal leukoencephalopathy; C1-INH, C1-esterase inhibitors.

^aAssociated more with plasma as replacement fluid.
suggested algorithm for treating acute rejection is presented in Figure 3.

**T Cell–Mediated Rejection**

The treatment of T cell–mediated rejection has changed little over time and few data exist comparing one strategy to another. Initial treatment conventionally includes pulse methylprednisolone at 250–500 mg daily for 3–5 days, as recommended by international guidelines (28). Treatment is ultimately guided by biopsy findings, with the majority of Banff class I lesions responding to methylprednisolone alone. T cell–mediated rejection involving lymphocytic infiltrate of the vasculature (Banff II and III lesions) generally requires T cell–depleting therapy, most commonly rATG dosed at 1.5 mg/kg for five to seven doses. One of the few randomized, controlled trials in this field compared rATG with horse anti-thymocyte globulin, showing superior effectiveness of rATG with a reversal rate of 88% versus 76% and an average total dose of 10 mg/kg (29). An updated Cochrane Database review published in 2017 concluded antibody therapy was superior to steroid therapy in reversing T cell–mediated rejection with no effect on subsequent acute rejection incidence or patient survival, noting most data were derived from studies during older immunosuppression eras where cyclosporine and azathioprine use was standard (30).

**Antibody-Mediated Rejection**

Similar to T cell–mediated rejection, few high-quality, randomized trials exist comparing treatment regimens for antibody-mediated rejection. In contrast to T cell–mediated rejection, however, several new therapeutic treatment options have been studied in recent years. Antibody-mediated rejection treatments are directed at removing antibody-producing B cells or plasma cells, removing antibodies (DSA), and/or inhibiting the subsequent complement-regulated graft damage (Figure 4). A systematic review by Roberts et al. (31) identified 12 comparative trials of antibody-mediated rejection treatment from 1950 to 2011, only five of which were randomized and three published in abstract form. These trials are small with a mean of 13 patients per arm with large degrees of heterogeneity including patients with both acute and chronic lesions. The authors report low-quality evidence supporting antibody removal therapies (plasma exchange,
immunoabsorption), and very low-quality evidence for all other treatments. A recently updated analysis included nine additional studies, four of which were randomized and three in abstract form, with similar conclusions (32). Nevertheless, plasma exchange and intravenous Ig (IVIG), with or without rituximab, was the most commonly used strategy and is generally considered standard of care for antibody-mediated rejection treatment (28,30,31). A typical regimen includes daily or every other day plasma exchange consisting of 1.5 plasma volume removal with each treatment followed by IVIG at 100–200 mg/kg, with or without a single dose of rituximab at 3.75 mg/m². Despite the limited data quality in this field, several studies are worth pointing out. Lefaucheur et al. (33) randomized 24 patients with antibody-mediated rejection to receive either monotherapy with IVIG at 2 gm/kg every 3 weeks× four doses or a more intensive regimen consisting of plasma exchange, IVIG, and two doses of rituximab. Patients receiving more intensive therapy experienced greater reduction in DSA with 92% graft survival at 3 years compared with 50% in those receiving IVIG alone. Although this study is small and does not necessarily confirm combination therapy with plasma exchange, IVIG, and rituximab as the best available therapy, the high rate of graft loss in the IVIG arm suggests a treatment regimen consisting only of IVIG is inadequate for most cases of acute antibody-mediated rejection. Sautenet et al. (34) attempted to clarify the utility of rituximab in combination with standard plasma exchange/IVIG therapy with the multicenter, blinded, randomized, placebo-controlled “Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation” (RITUX-ERAH) trial. Thirty eight patients with antibody-mediated rejection received three doses of plasma exchange plus IVIG before undergoing randomization to rituximab 375 mg/m² (n=19) or placebo (n=19), followed by two additional plasma exchange/IVIG treatments in each group. There was no difference in the composite primary outcome of graft loss or improvement in graft function at day 12; however, a large crossover between groups limits accurate interpretation of these data, with eight of 19 patients in the placebo arm receiving rituximab as rescue therapy for insufficient treatment efficacy.

Several small series have evaluated alternative agents for antibody-mediated rejection refractory to “standard” treatment regimens. Bortezomib, an US Food and Drug Administration approved proteasome inhibitor for treatment of multiple myeloma, has received special focus because of its ability to induce apoptosis in antibody-producing plasma cells; however, there is minimal effect on DSA burden when used as a sole agent (35,36), with mixed results when used in combination with plasma exchange/IVIG (37–39). A recent case series describes successful reduction in plasma cell infiltrate and stabilization of graft function after treatment with bortezomib in several patients with plasma cell-rich acute rejection, a rare histologic finding historically associated with poor outcomes despite aggressive treatment (40). The humanized mAb eculizumab has been targeted in the prevention (41) and treatment (42) of antibody-mediated injury because of its mechanism of complement component C5 inhibition. In a small series, Orandi et al. (42) evaluated outcomes of 24 patients with severe antibody-mediated rejection after desensitization for positive crossmatch kidney transplant treated with either splenectomy (n=14), eculizumab (n=5), or combination splenectomy and eculizumab.
(n=5). At 1 year, four of 14 and four of five patients experienced graft loss in the splenectomy and eculizumab groups, respectively, whereas those treated with combination splenectomy and eculizumab experienced no graft loss and minimal transplant glomerulopathy on protocol biopsy. Not surprisingly this aggressive regimen is not without risk, with high rates of infection (urinary tract infection, bacteremia/sepsis, pneumonia) in those undergoing combination therapy. A pilot study of the anti-IL six receptor antibody tocilizumab has shown promising results for patients with chronic antibody-mediated rejection (43), a disease for which there is currently no proven treatment; however, this agent has not been studied in the treatment of acute antibody-mediated rejection.

Lastly, C1-esterase inhibitors (C1-INH) have recently been studied in two small studies for the treatment of acute antibody-mediated rejection (44,45). C1-INH inhibits proximal enzymes in the classic complement pathway including C1q, and reports of poor outcomes after detection of C1q-binding DSA (46) provide further rationale for its use in antibody-mediated rejection. In a single-arm pilot study, Viglietti et al. (45) treated six patients with antibody-mediated rejection deemed non-responsive to conventional treatment, with all patients showing improvement in GFR at 6 months and a decrease in C4d deposition from baseline (five of six patients) to month 6 (one of six patients). Montgomery et al. (44) randomized 18 patients with antibody-mediated rejection to either C1-INH at 20,000 U every other day for 2 weeks or placebo, in addition to standard therapy including plasma exchange, IVIG, and rituximab. There was no difference in the primary end point of graft loss or histology at 20 days; however, out of 14 patients with biopsies at 6 months, three of seven patients receiving placebo versus zero of seven patients receiving C1-INH showed transplant glomerulopathy. There is currently one ongoing randomized, clinical trial comparing C1-INH with placebo in patients with antibody-mediated rejection receiving standard of care (Clinicaltrials.gov identifier NCT03221842); however, another was recently terminated because of lack of efficacy (Clinicaltrials.gov identifier NCT02547220).

Subclinical Rejection

The identification and treatment of alloimmune responses before the onset of clinical graft dysfunction may theoretically minimize the development of chronic lesions that ultimately lead to graft loss (47,48). This approach involves protocol biopsy of stable grafts or the use of screening biomarkers such as DSA to identify patients at risk for subclinical immunologic lesions. The incidence of subclinical T cell–mediated rejection in the modern era of immunosuppression is low (49), and long-term outcomes do not appear to be as severely affected compared with subclinical antibody-mediated rejection (50). In 121 patients treated with tacrolimus, mycophenolate mofetil, and prednisone and randomized to protocol versus indication-only biopsies, the incidence of subclinical T cell–mediated rejection was only 5%, with no difference in graft function at 6 months (49) despite those with subclinical rejection receiving treatment. Subclinical antibody-mediated rejection, in contrast, represents an attractive therapeutic target given the attributed poor long-term outcomes (50), likely via progression to chronic antibody-mediated rejection over time (47,51). Using DSA as a biomarker, studies have shown approximately 50% of patients with stable function and de novo DSA will show evidence of subclinical antibody-mediated rejection on biopsy (47,51–53). Despite the risk of poor outcomes associated with subclinical antibody-mediated rejection, few data exist to suggest treatment intervention will alter the clinical course. Orandi et al. (54) published a retrospective analysis of 77 patients with subclinical antibody-mediated rejection diagnosed by protocol biopsy, 54% of which received treatment with various combinations of plasma exchange, IVIG, rituximab, and eculizumab. With a mean follow-up of 5.2 years, overall rates of graft loss were similar between those treated and untreated. However, when compared with matched controls, treated patients experienced a lower risk of graft loss versus untreated patients (hazard ratio, 1.73 [P = 0.21] versus 3.34 [P = 0.01], respectively). Thus, although the prospect of identifying subclinical antibody-mediated rejection before clinical dysfunction remains attractive, more data are needed before concluding that treatment of this population will improve the long-term clinical course.

Conclusions

Despite historically low acute rejection rates thanks to increasingly effective immunosuppressive protocols, acute rejection episodes continue to affect graft survival and prompt recognition and treatment is crucial. When feasible tissue biopsy should be performed in any patient with unexplained acute graft dysfunction, and accurate assessment of immunologic risk can assist in determining the need for tissue diagnosis. The Banff criteria for diagnosing antibody-mediated rejection continue to evolve and no longer require the combination of DSA and C4d deposition, with several new agents under investigation for treatment. Identifying subclinical antibody-mediated rejection provides an opportunity to intervene before the onset of clinical dysfunction; however, further clinical data are needed to determine if treatment will alter clinical outcomes.

Disclosures

Dr. Cooper has nothing to disclose.

References


