Incidence of Humoral Rejection in Heart Transplant Recipients Treated With Tacrolimus or Cyclosporine A


Humoral rejection is a rare but potentially fatal form of acute allograft rejection. Pathophysiologically, allosensitization against graft determinants occurs either pre- or posttransplantation. Preformed antibodies lead to the phenomenon of hyperacute rejection. The de novo synthesized antibodies directed against HLA antigens expressed on graft endothelium are clearly associated with humoral rejection. The diagnosis is made by histologic criteria of endothelial swelling and vasculitis and by immunohistologic demonstration of deposition of complement split products.

This study was designed to explore the incidence of humoral rejection in human heart transplant recipients treated either with cyclosporine A (CyA) or tacrolimus (FK506). As a marker for humoral rejection, C4d complement fragment was used, originally described in kidney allografts, which we introduced as a marker for the diagnosis of acute humoral rejection in heart transplantation.

METHODS

A total of 109 endomyocardial biopsies (EMB) of 45 consecutive patients within 3 months posttransplantation were immunohistochemically investigated for deposition of complement split product C4d. All patients received steroids and azathioprine. Twenty patients were treated with FK506 and 25 patients received CyA. No induction therapy was given. C4d staining was semiquantitatively graded by two blinded investigators. EMB were assigned C4d+++ when all capillaries were stained, C4d++ indicates segmental, C4d+ scarce, and C4d− absent staining.

RESULTS

Table 1 depicts the numerical distribution of the endomyocardial biopsies among the C4d subgroups. Patients were assigned to each group according to their maximal score in any biopsy investigated. There was no statistical difference found for severe humoral rejection (C4d++++) between the two treatment groups. Seventeen of 25 (68%) CyA patients showed complement deposition (C4d+, C4d++, C4d++++) versus 10 of 20 (50%) FK506 treated patients. This overall deposition of C4d also was statistically not different between the two groups (χ²; P > .05); however, there was a tendency for more frequent complement deposition in the CyA group. The association between C4d+++ and fatal clinical outcome was significant (Fisher exact; P < .05); however, there was again no significant difference between the two treatment groups.

CONCLUSION

Immunosuppressive regimens consisting of glucocorticosteroids, azathioprine, and either CyA or FK506 were not capable of preventing humoral rejection. The large number of patients with humoral rejection is consistent with other reports. With the limited number of patients, a significant difference for complement activation (C4d++; C4d+++; C4d++++) between the two treatment groups was not found. In addition, severe humoral rejection (C4d++++) was not different between the two groups. However, there was a trend towards more frequent complement deposition in patients treated with CyA. CyA and FK506 are primarily directed against the activation of T lymphocytes by inhibiting the synthesis of interleukin-2. The synthesis of antibodies as a first step towards humoral rejection by B lymphocytes and the subsequent activation of the complement cascade via the classical pathway is thus not suppressed.

Whether FK506 may have weak additional properties as compared to CyA to suppress a humoral immune response directed against a human cardiac allograft needs to be verified with a larger patient cohort. New immunosuppres-
sive drugs must be explored to effectively suppress humoral rejection in the setting of human heart transplantation.

REFERENCES