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Antithymocyte globulin induction therapy for adult heart transplantation: A UK national study

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BACKGROUND: Induction therapy with antithymocyte globulin (ATG) after heart transplantation (HTx) has never been assessed in a placebo-controlled randomized trial. We investigated trends in use of ATG and its relationship to outcome after HTx in a national cohort.

METHODS: Between July 1995 and March 2008, 2,151 adult HTxs were performed. Patients given OKT3 or an interleukin-2 receptor antagonist, repeat transplants, heterotopic, and multi-organ transplants were excluded, leaving 2,086 HTx for analysis. Of these, 1,143 (55%) received induction with ATG.

RESULTS: The proportion of patients given ATG increased from 26% in June 1995 to 75% in August 2007 ($p < 0.01$). The age and gender distributions of recipients and donors were similar in the ATG and non-ATG groups. Survival to 10 years was similar: 56.2% in the non-ATG group vs 55.9% in the ATG group ($p = 0.95$). The number of treated rejection episodes in the first year was lower in the ATG group (incidence rate ratio, 0.76; 95% confidence interval [CI], 0.68–0.85, $p < 0.01$), but the number of infective episodes was higher (incidence rate ratio, 1.18; 95% CI, 1.00–1.39, $p = 0.048$), and these differences remained after risk adjustment, with an adjusted incidence rate ratio of 0.85 (95% CI, 0.75–0.95, $p < 0.01$) and 1.21 (95% CI, 1.02–1.44; $p = 0.027$). Deaths due to infective causes were higher in the ATG group ($p = 0.03$).

CONCLUSION: There has been a trend towards an increased use of induction therapy. There was no change in overall survival, but ATG induction was associated with a decreased incidence of rejection and an increase in infection.

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Heart transplantation (HTx) has become an established treatment for advanced heart failure. The introduction of cyclosporine resulted in a significant improvement in short-term and long-term patient survival after transplantation.[1] Cyclosporine is an effective immunosuppressive agent, but it is nephrotoxic and can cause acute renal injury and chronic kidney disease, which has become one of the most frequent long-term complications of organ transplantation.[2]

Antithymocyte globulin (ATG), a polyclonal antilymphocyte preparation that selectively depletes T lymphocytes,[3,4] has been used as an induction agent during renal transplantation and was effective in reversing acute renal

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allograft rejection.[5,6] ATG induction also reduced early rejection episodes after HTx.[7] Some institutions use biologic induction agents, including ATG, muromonab-CD3, or a monoclonal antibody against the interleukin IL-2 receptor (IL-2R), with the aim of (1) delaying the introduction or reducing the dose of cyclosporine or tacrolimus, thereby reducing nephrotoxicity[8,9]; (2) achieving more robust immunosuppression during the early postoperative period[10]; and (3) reducing or delaying the incidence of acute rejection.[8,11] Although there have been a number of studies of ATG as an induction agent,[12–15] none of these investigations have been in the form of placebo-controlled trials.

The aim of this study was to use a comprehensive national transplant database to examine the pattern of use of ATG as an induction agent after cardiac transplantation in the United Kingdom (UK) and to examine its effect on rejection, infection, and patient survival.

Methods

The UK Cardiothoracic Transplant Audit is an ongoing prospective cohort study involving all UK HTx centers, which has collected data on all patients listed for HTx and patients who received allografts since April 1995. Data accrual is obligatory, and follow-up for survival is 100%.

Study population

Adults (age $\geq$ 16 years) receiving an isolated first time orthotopic HTx between July 1995 and March 2008 in the UK were included. Exclusions were 527 pediatric transplant patients, 37 retransplants, 19 multi-organ transplants, 31 heterotopic transplants, and 15 patients who were given induction therapy with an IL2R antibody or monomurab-CD3 (OKT3). After exclusions, the study population consisted of 2,086 patients.

Data collection

Audit data, collected at listing, at transplant, at 3 months, and annually thereafter until the patient's death, are processed by National Health Service Blood and Transplant (NHSBT) and submitted monthly to the audit. This study uses data supplied at the end of June 2009. Initially, data were collected on the basis of presumed consent, but more recently, informed consent has been sought when listing the patient for transplantation. In the UK, audit projects do not require separate research ethics committee approval.

Estimated glomerular filtration rate

Serum creatinine levels were not routinely recorded during the first year of the audit. Therefore creatinine and estimated glomerular filtration rate (eGFR, ml/min/1.73m^2) calculations excluded patients who received allografts in the first year (July 1995 through March 1996). The eGFR was calculated using the 4-variable Modification of Diet in Renal Disease formula (MDRD): eGFR (MDRD) = 32788 $\times$ serum creatinine (measured in μmol/liters)$^{-1.154}$ $\times$ age$^{-0.203}$ $\times$ [1.210 if black] $\times$ [0.742 if female].

Statistical methods

Continuous variables were summarized using mean and standard deviation or median and interquartile range, as appropriate, and categoric measures were reported as a number and percentage. Groups were compared using the t test, Wilcoxon rank sum, or chi-square tests as appropriate. Survival was estimated by the Kaplan-Meier method and evaluated using the log-rank test. Adjusted survival estimates were obtained using Cox proportional hazards regression. Adjustment was made for factors that have been identified in previous UK analyses, including recipient age, gender, diagnosis, body mass index (BMI), preoperative state (in-hospital, on inotropes, ventilated), comorbidity (diabetes, vascular disease, previous open heart surgery, anti-arrhythmics, creatinine clearance at transplant), and donor age, gender, size, cause of death, ischemia time, donor-recipient size, and cytomegalovirus mismatch, history (diabetes, drug abuse). The cumulative incidence of different causes of recipient death was estimated in the presence of competing risks.

Adjusted rates of rejection and infection in the first year were estimated using negative binomial regression. Factors adjusted for were identified from a review of the literature[2] and included recipient age, gender, ethnicity, ventricular assist device (VAD) insertion before surgery, recipient comorbidity (diabetes, hypertension creatinine clearance at HTx), and ischemia time. Renal function to 2 years was modeled using linear mixed effects regression with pre-HTx and post-HTx values modelled jointly. The analyses were adjusted for recipient age, gender, comorbidity (diabetes, hypertension creatinine clearance at transplant), and female donor, the effects of which were allowed to vary with time after transplant. Treatment by time interactions was also modeled. Log transformation was used to normalize the data and so the results are reported as geometric means. For all outcomes, changes with calendar time were examined by adding interaction terms to the model. Analyses were done using Stata 11.2 (StataCorp LP, College Station. TX) and SAS 9.2 (SAS Institute, Cary, NC) software.

Results

Recipient and donor characteristics

A total of 2,086 eligible adults underwent HTx in the study period. Overall, 1,143 patients (55%) received ATG induction therapy at the time of HTx. The use of ATG increased over time from 26% in 1995 to 1996 to 76% in 2007 to 2008 ($p < 0.01$, Figure 1). Patient demographics and comorbidities are reported in Table 1. The proportion of non-ambulatory heart failure patients and the proportion of patients of non-white ethnicity was higher in the ATG group. There were proportionally more patients with dilated cardiomyopathy (DCM) and fewer with ischemic heart disease (IHD) in the ATG group; eGFR was similar in the 2 groups, as was the proportion of patients with an eGFR of less than 60 ml/min/1.73 m^2. Donor demographics were similar in the