TOPIC

Timing of the First Endomyocardial Biopsy in Heart Transplantation after Induction Immunosuppressive Therapy. Experience from Canadian Heart Transplant Centre

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ABSTRACT

Background. The exact time point at which the first endomyocardial biopsy could be safely performed after the heart transplantation has not been systematically studied. In an attempt to determine this time point in our population, the number and severity of acute rejection episodes in the first eight weeks after the heart transplantation were assessed in 91 patients who underwent the procedure at St Paul's Hospital, Vancouver, between September 1996 and December 2002.

Methods and Results. For the purpose of our analysis, acute rejection was defined as the grade ≥2 according the International Society for Heart and Lung Transplantation (ISHLT). Three hundred and sixty two endomyocardial biopsies were performed in 87 patients surviving to the first biopsy from one to eight weeks after the heart transplantation.

In 85 patients who received induction immunosuppressive therapy, 13 episodes of acute rejection were identified. In two patients who did not receive the induction therapy, three episodes of acute rejection occurred. Acute rejection grade ISHLT 3 was found in 2 patients who did not receive induction therapy and in three patients who did. ISHLT grade 4 rejection occurred at weeks 5 and 7 in two patients who received induction therapy. Only one patient who received induction therapy had acute rejection within the first three weeks after the heart transplantation.

Conclusions. Our analysis reveals that the frequency of acute rejection within the first eight weeks after the heart transplantation using induction therapy is low in this cohort, suggesting that the first routine endomyocardial biopsy could be delayed until the week four post-transplant.

Key words: heart transplantation, endomyocardial biopsy.

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Endomyocardial biopsies (EMBx) are performed for routine surveillance after the heart transplantation (HTx) and they remain the gold standard for diagnosis of acute cardiac allograft rejection (AR). The first EMBx is usually performed between the 10th and 14th day post-HTx if induction therapy (ITx) was used and earlier if the ITx was not used (1).

There are no clinical trials assessing the optimum timing and frequency of EMBx (2, 3). ITx is known to reduce the requirement for high-dose steroids and early high doses of calcineurin inhibitor. Polyclonal antibody ITx is effective in both prophylaxis and treatment of rejection but it can lead to an increased risk of opportunistic infection and malignancies (4). Monoclonal antibody ITx was developed to target highly specific components of the rejection pathway thereby reducing the risk of infection and malignancy and it has been shown to be effective in reducing early rejection after HTx (5, 6). The purpose of this review was to identify the number and severity of acute rejection episodes (AR) in the first eight weeks post-HTx at St Paul's Hospital, Vancouver, British Columbia, in order to assess the risks and benefits of delaying first EMBx.

MATERIALS AND METHODS

Demographic EMBx data on 91 *de novo* patients who received HTx between September1996 and December 2002 were reviewed using retrospective chart review and data extracted from the British Columbia Transplant Society (BCTS) Database. Four patients died before first EMBx, none of these deaths were attributed to AR.

In the cohort of the remaining 87 patients, 74 (85%) were men and 13 (15%) were women and the mean age was 53±11 years. Two patients did not receive ITx. Seventy-nine patients received polyclonal antibody induction therapy using rabbit anti-human thymocyte immunoglobulin (Thymoglobuline – Imtix, Sangstat) (r-ATG). 2 patients received humanized monoclonal antibody therapy with basiliximab (Simulect®) and 4 patients received both. ATG was

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Tab. 1. Patients' characteristics

Age	**n = 87** 52.8 ±11.4 (32–72)
Men/women	74/13
Induction therapy: ATG/basiliximab/both/none	76/ 2/ 4/ 2
Aetiology of CHF: ischemic/non-ischemic	42/49

Legend:
ATG – antithymocyte immunoglobulin, CHF – chronic heart failure

Tab. 2. ISHLT Grading System for Endomyocardial Biopsies

Grade	Severity of infiltrate	Presence of myocyte injury
0	No evidence	No evidence
1A	Focal perivascular or intersticial	No injury
1B	Multifocal or diffuse	No injury
2	Single focus or dense	With myocyte injury
3A	Multifocal dense infiltrates	With injury
3B	Diffuse dense infiltrates	With injury
4	Diffuse and extensive infiltrate	With injury

Tab. 3. Results

Days post HTx	0–7	8–14	15–21	22–28	29–35	36–42	43–49	50–56
No. of Bx	14	45	62	66	48	50	36	41
No.≥ 2 ISHLT	2	2	0	3	4	1	2	2
≥2 with ITx	0	1	0	3	4	1	2	2
≥2 without ITx	2	1	0	0	0	0	0	0

Legend:
HTx – heart transplantation, No. – number, Bx – endomyocardial biopsy, ISHLT – Grading System for Endomyocardial Biopsy, ITx – induction therapy

given for 3 days at dose 2mg/kg daily to maximal dose of 150 mg per day and basiliximab was given on the day 0 and 4 at dose 20 mg. Patients characteristics are shown in Tab. 1.

AR was defined as International Society for Heart and Lung Transplantation (ISHLT) grade ≥2 (7). ISHLT Grading System for EMBx is shown in Tab. 2.

RESULTS AND DISCUSSION

Three hundred and sixty two EMBx were performed in 87 patients during the first 8 weeks after HTx. In 85 patients who received ITx, 13 episodes of AR were found. In two patients who did not receive ITx, three episodes of AR occurred. Grade 3 AR was found in two patients who did not receive ITx, two patients who received ATG and one patient who received basiliximab. ISHLT grade 4 AR occurred at weeks five and seven in two patients who received ATG. Only one patient who received ITx had an episode of AR within first three weeks post HTx (Tab. 3). These retrospective data show that the frequency of AR within first 8 weeks post-HTx using ITx is low in this cohort. Result do not justify delaying the first EMBx until confirmed by prospective analysis of HTx patients treated only with monoclonal ITx.

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COMMENTARY

On Málek F. et al: "Timing of First Endomyocardial Biopsy in Heart Transplantation after Induction Immunosuppressive Therapy. Experience from Canadian Heart Transplant Centre"

Rejection in cardiac transplantation is a frequent complication in the first months after the transplantation (Tx) (1). Most episodes are characterized by the infiltration of the transplant by activated lymphocytes, which eventually damage myotic fibers. If the rejection episode is treated in time, it will heal without causing large damage to the allograft. So far the only method that can reliably detect the early stages of rejection is right ventricular endomyocardial biopsy (EMB). This method is still difficult to replace and it is applied according to the protocol adopted by the Stanford centre as early as the 1970s. As the reviewed study correctly states, it seems that the original scheme, according to which EMB is performed early - one week after Tx - may be modified. The designed induction prophylaxis procedures (also described in the paper) allow the bridging of the early post-transplantation period, when risk of rejection is highest, yet renal function disorder does not allow full employment of calcineurin inhibitors (cyclosporin A or tacrolim). Indeed, there have been no studies on the timing of the first biopsies according to the biopsy protocol in patients in whom induction therapy is applied.

In the last three years, cyclosporin, mycophenolate mofetil (MMF), prednisone and polyclonal antilymphocytic globulins have been the most commonly used immunosuppressives.

According to the international register, in 1992-2002, early transplant rejection (in patients who died within 30 days) accounted for a mere 6.4% (2) among the causes of death, i. e. for only a very small part. The dominant causes are primary failure of the allograft (16.4 %), multiple organ failure (13.9 %), and infection (14.2%). Patients are admitted to hospital because of rejection most often during the first year after the transplantation; this applies to approximately 11% of the patients.

The work of Málek and colleagues has shown that during induction prophylaxis (most commonly with polyclonal antilymphocytic globulins) cellular rejection within the first 3 weeks does not practically occur. This finding has a practical implication – performing an EMB during the first weeks after Tx is not completely without risk (the most common complication of jugular vein puncture is pneumothorax) and presents some discomfort for the patient. Frequently repeated biopsies may even lead to damage of the tricuspid valve and to insufficiency, which is then one of the factors in an unfavorable course.

It seems that endomyocardial biopsy is losing its exclusive position amongst methods used for reliable diagnosis of rejection. This view is justified by the improved survival of individuals and simultaneous decrease of the percentage of fatal rejections. At most centres, one-year survival rates exceed 80%. The work of Málek et al. provides a valuable guide for the modification of the early biopsy scheme and delay of the first investigation.

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