

Brief report

Repeated Daclizumab Administration to Delay the Introduction of Calcineurin Inhibitors in Heart Transplant Patients With Postoperative Renal Dysfunction

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ABSTRACT

Daclizumab is an interleukin-2 receptor antagonist which is used for induction therapy in heart transplant patients. It has few side effects and is associated with a low infection rate. Postoperative renal failure after heart transplantation is common and potentially fatal. The administration of calcineurin inhibitors in the postoperative period can aggravate the situation. We report the cases of six patients who underwent heart transplantation and developed acute renal failure in the immediate postoperative period. All were administered daclizumab weekly to avoid the introduction of calcineurin inhibitors and to facilitate recovery of renal function. Calcineurin inhibitors were introduced only once renal function had improved. Renal function recovered in all cases and there was a low complication rate. The administration of repeated doses of daclizumab to patients who experience acute postoperative renal failure after heart transplantation may provide an alternative therapeutic approach that enables calcineurin inhibitors to be avoided and, consequently, renal function to recover.

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Dosis repetidas de daclizumab para retrasar la instauración del inhibidor de la calcineurina en pacientes con trasplante cardíaco y disfunción renal postoperatoria

RESUMEN

El daclizumab es un antagonista del receptor de la IL-2 usado como terapia de inducción en el trasplante cardíaco con pocos efectos secundarios y baja tasa de infecciones. La insuficiencia renal postoperatoria tras un trasplante cardíaco es frecuente y potencialmente grave. La introducción de los inhibidores de la calcineurina en el postoperatorio puede agravar esta situación. Presentamos 6 casos de pacientes sometidos a trasplante cardíaco y que desarrollaron insuficiencia renal postoperatoria. En todos ellos se administró daclizumab de forma semanal para evitar la introducción del inhibidor de la calcineurina y permitir la recuperación renal. Una vez mejorada la función renal, se introdujo el inhibidor de la calcineurina. En todos los casos se recuperó la función renal y la tasa de complicaciones fue baja. La administración de dosis repetidas de daclizumab en pacientes con insuficiencia renal tras un trasplante cardíaco puede ser una alternativa para evitar el uso de inhibidores de la calcineurina y permitir así la recuperación de la función renal.

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INTRODUCTION

Daclizumab is an interleukin-2 (IL-2) receptor antagonist used for induction therapy in heart transplantation (HT) patients. In terms of mortality, it is no better than induction therapies like antithymocyte thymoglobulin or OKT3, but the adverse effects are fewer and it is better tolerated.^{1,2} In fact, it does not increase

infection rates and its use has not led to reported adverse effects of any note.

Currently, IL-2 receptor antagonists are the most commonly used induction therapy in HT. This widespread use has been encouraged by improved knowledge of the drugs and has led to their administration in abnormal situations.³

Acute renal insufficiency (ARI) in the postoperative period occurs with some frequency in HT and is associated with patient-related factors, prior clinical status, prolonged surgery time, and acute graft failure. In most protocols calcineurin inhibitors (CNIs) are introduced at 2–3 days post-transplantation. In certain instances of kidney failure, this can lead to a serious risk of

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aggravation that may worsen the recently-transplanted patient's prognosis.

Our working hypothesis was that weekly repeated doses of daclizumab could protect patients from acute rejection without needing to administer a CNI.

The objective of the present article is to present our experience of daclizumab use in HT patients with postoperative ARI in order to delay introducing CNI and facilitate renal function recovery.

METHODS

We describe our experience with 6 patients who underwent HT at our center and subsequently developed postoperative ARI which led to administering repeated doses of daclizumab until recovery of renal function.

RESULTS

Patient characteristics at HT and clinical evolution are in Table 1.

All but one patient (P2) were urgent transplant recipients; 4 received extracorporeal membrane oxygenation (ECMO) support. All patients developed ARI in the immediate postoperative period before sufficient time had passed for them to receive a CNI dose in line with the standard protocol. All other immunosuppressive drug treatments were administered as the protocol.

Three patients (P1, P5 and P6) required ultrafiltration (UF) in the immediate postoperative period and one (P5) underwent transplantation with UF. The others recovered renal function with more conservative measures.

In all patients, daclizumab was first administered within hours of HT and weekly after that (1 mg/kg/intravenous), following the standard protocol. Later, the same dose was administered every 7 days until recovery of renal function. Daclizumab was last administered on the same day that the low-dose CNI regimen began. One patient (P2) received 3 doses of daclizumab, 4 patients (P1, P3, P4 and P6) received 4, and 1 patient (P5), 5. Except in P2 and P6, a CNI was administered from postoperative week 3.

Three patients developed infectious complications in-hospital and mycophenolate mofetil (MMF) was reduced to 1500 mg/day. Patient P3 developed a sternal wound infection after intensive care (IC); P4, asymptotically, and despite prophylaxis (donor +/- recipient -), presented high cytomegalovirus (CMV) viral load and

was administered therapeutic doses of valgancyclovir. Patient P5 developed *Acinetobacter* spp. pneumonia which complicated and lengthened their IC stay but was finally resolved with no after-effects.

No other complications of note arose in any patient.

DISCUSSION

The present study supports the use of IL-2 receptor antagonists like daclizumab in dealing with postoperative ARI following heart transplantation. This drug protects the myocardium from rejection, which enables us to delay introducing a CNI.

Acute renal insufficiency in the immediate postoperative period following HT is frequent, especially in recipients of urgent transplantation. In our study, most patients were transplanted with ECMO support. This enabled us to stabilize and in some cases improve their critical clinical condition prior to transplantation. In this series, most patients presented with slightly elevated creatinine. This could be considered a contraindication for HT. However, in all cases we believed we were dealing with prerenal ARI due to low cardiac output and, therefore, recoverable following transplantation.

CNIs are the first choice drugs in maintenance immunosuppression therapy. They produce acute vasoconstriction of the afferent arteriole in the renal glomeruli and reduce renal blood flow. The global deterioration of renal function following CNI introduction materializes as a slight increase in creatinine that is usually temporary and depends on the dosage. However, in cases of low cardiac output and/or prior renal deterioration, the harmful effect on renal function can be greater and may complicate the patient's clinical course.

Daclizumab is a powerful induction drug but its efficacy as maintenance therapy is unknown. Initial studies involved therapy consisting of 5 doses every 2 weeks post-HT, in addition to standard immunosuppression therapy. The current trend is to reduce the number of doses as studies indicate 2 doses are sufficient.⁴ Single-center studies in other organs indicate use of daclizumab could help delay introducing a CNI in patients with ARI.⁵ Empirically, we considered one 1 mg/kg/week of daclizumab, in a single dose, would provide adequate patient protection.

The strategy we followed in our patients consisted of maintaining normal dosage of other immunosuppressive drugs (MMF and steroids). However, MMF dosage was reduced in presence of infection. The immunosuppressive effect of daclizumab enabled

Table 1
Patient Characteristics

Patient	Age	Gender	Etiology	HT code	Pre-HT Cr	Maximum Cr	UF	CNI introduction (day post-HT)	No. doses daclizumab	Cr at discharge	Results 1st ^a biopsy and day post-HT	Infections	Days ICU
1	57	Man	Ischemia	Urgent, ECMO	2.1	2.6	Yes, 96 h	14	4	1	1 R (17)	No	15
2	62	Man	Ischemia	Elective	2.5	3.2	No	7	3	1.8	2 R (12)	No	4
3	63	Man	Ischemia	Urgent, ECMO	1.4	2.8	No	14	4	1.5	2 R (19)	Yes, late sternal infection	16
4	51	Woman	Alcohol-induced IDC	Urgent, ECMO	2.1	3.4	No	16	4	0.7	2 R (24)	Yes, early CMV therapy	17
5	53	Woman	IDCi	Urgent, ECMO	HD pre-TC	HD	Yes, 120 h	18	5	1.2	1 R (43)	Yes, <i>Acinetobacter</i>	49
6	42	Woman	HCM	Urgent	1.4	2.5	Yes, 96 h	12	4	1	2 R (15)	No	12

CMV, cytomegalovirus; CNI, calcineurin inhibitors; Cr, creatinine; ECMO, extracorporeal membrane oxygenation; HCM, hypertrophic cardiomyopathy; HD, hemodialysis; HT, heart transplantation; IDC, idiopathic dilated cardiomyopathy; ICU, intensive care unit; UF, ultrafiltration.

Immunosuppression protocol: all patients received steroids (day 1, 125 mg/8 h methylprednisolone followed by 1.2 mg/kg/day deflazacort, reduced to 0.3 mg/kg per week) and mycophenolate mofetil (2 g/day) from day 2.

us to delay introducing CNI. In the series presented, the second dose was administered at 7 days post-HT.

The complications that developed (Table 1) were controllable and did not seriously harm the patients' physical condition. After HT, a portable echocardiograph was used daily to evaluate indirect signs of rejection in all patients, but none were observed.

Four patients showed 2R rejection in the first biopsy and were treated with corticoid bolus. In all cases, a control biopsy showed rejection had been resolved. No patient suffered clinical rejection and the discharge echocardiogram was normal in all cases.

The infectious complication rate was low considering the type of patient involved. Only P5 (the patient who present the worst condition at transplantation) developed a serious infectious complication during the postoperative period. Other infections were one asymptomatic for CMV (donor +/recipient –) despite appropriate prophylaxis, and one late sternal wound complication.

We think that the repeated daclizumab administration protocol we followed with these patients could be an alternative therapeutic approach in postoperative ARI. All postoperative complications were controllable and some were more attributable to the patients' poor condition than to the protocol. Rejection observed in biopsies of four patients can be attributed to the diminished immunosuppressive effect of daclizumab but in no case did clinical conditions or hemodynamic deterioration occur.

Daclizumab is no longer commercially available and the only IL-2 receptor antagonist is basiliximab. Recent experience has shown it is equally suitable to delay introducing CNI.⁶

On the basis of these data, we think repeated daclizumab administration in ARI following heart transplantation, as a means of avoiding the introduction of the CNI, is a possible alternative therapeutic approach that favors renal function recovery with a complication rate of no significance.

CONFLICTS OF INTEREST

None declared.

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