

Use of a “CNI holidays” strategy in acute renal dysfunction late after heart transplant. Report of two cases

Pau Alonso, Ignacio Sanchez-Lazaro, Luis Almenar, Luis Martinez-Dolz, Ana Andres, Antonio Salvador, Anastasio Montero

Department of Cardiology, La Fe University Hospital Valencia, Valencia - Spain

ABSTRACT

Background: Acute renal dysfunction (ARD) may appear in heart transplant (HTx) patients both in the early postoperative period and during follow-up, even after several years. CD25 is a subunit of the interleukin-2 receptor which is found exclusively on activated CD4 T lymphocytes. CD25 is crucial for clonal expansion of anti-allograft host lymphocytes that mediate in acute rejection. There are experiences supporting the use of Anti-CD25 monoclonal antibodies (MAb) immediately after HTx in patients with ARD as a bridge to renal function recovery, allowing the temporary suspension of treatment with CNI.

Methods: In this study we report two cases of successful use of weekly MAb (basiliximab) in HTx patients who developed late ARD after HTx.

Conclusions: In conclusion, we think that in cases of ARD where CNI therapy plays a key role, the use of weekly doses of basiliximab allows CNI discontinuation until the restoration of renal function is achieved.

Keywords: Basiliximab, CNI holiday, Heart transplant

Introduction

Chronic kidney disease (CKD) is a well-known complication after heart transplant (HTx) and is associated with an increased long-term morbidity and mortality (1, 2). Calcineurin inhibitor therapy (CNI) has been implicated as a principal cause of post-transplantation renal dysfunction (3, 4). Furthermore, renal disease before transplantation, perioperative hemodynamic insults to the kidneys, nephrotoxic effects of other drugs, dyslipidemia, hypertension and diabetes mellitus can all contribute to chronic renal failure.

Acute renal dysfunction (ARD) may appear in cardiac transplant patients both in the early postoperative period and during follow-up, even after several years. ARD during the follow-up period is common and has been related with patient conditions (i.e., diarrhea, CKD), immunosuppressive drugs—mainly CNIs—and other treatments.

Anti-CD25 monoclonal antibodies (MAbs), basiliximab and daclizumab, have shown to reduce the incidence of acute rejection after heart transplantation (5). Furthermore, there are

experiences supporting the use of these drugs immediately after HTx (6) in patients with ARD as a bridge to renal function recovery, allowing the temporary suspension of treatment with CNI.

In this study we report two cases of successful use of MAb (basiliximab) in patients who developed late ARD after HTx.

Case Report

Case 1

We here present the case of a 77-year-old male who underwent HTx in 2002 due to an ischemic cardiomyopathy. Induction therapy was done with OKT3, while tacrolimus (Tac), mycophenolate mofetil (MMF) and deflazacort were used as maintenance immunosuppressive agents. Immediate postoperative progress was favorable. During the first year, the patient suffered only one asymptomatic rejection (treated with corticosteroids) with a normal left ventricular function. Preemptive therapy with ganciclovir was given due to an asymptomatic elevation of cytomegalovirus load. The coronary angiography with intravascular ultrasound performed 12 months after HTx showed no lesions. There were no more complications in the first year.

During the first six years the patient remained asymptomatic but, after observing a worsening of renal function without proteinuria (Cr 2.75 mg/dL), Tac was replaced by Everolimus (Eve 0.75 mg bid). Renal function then recovered (Cr 1.25 mg/dL).

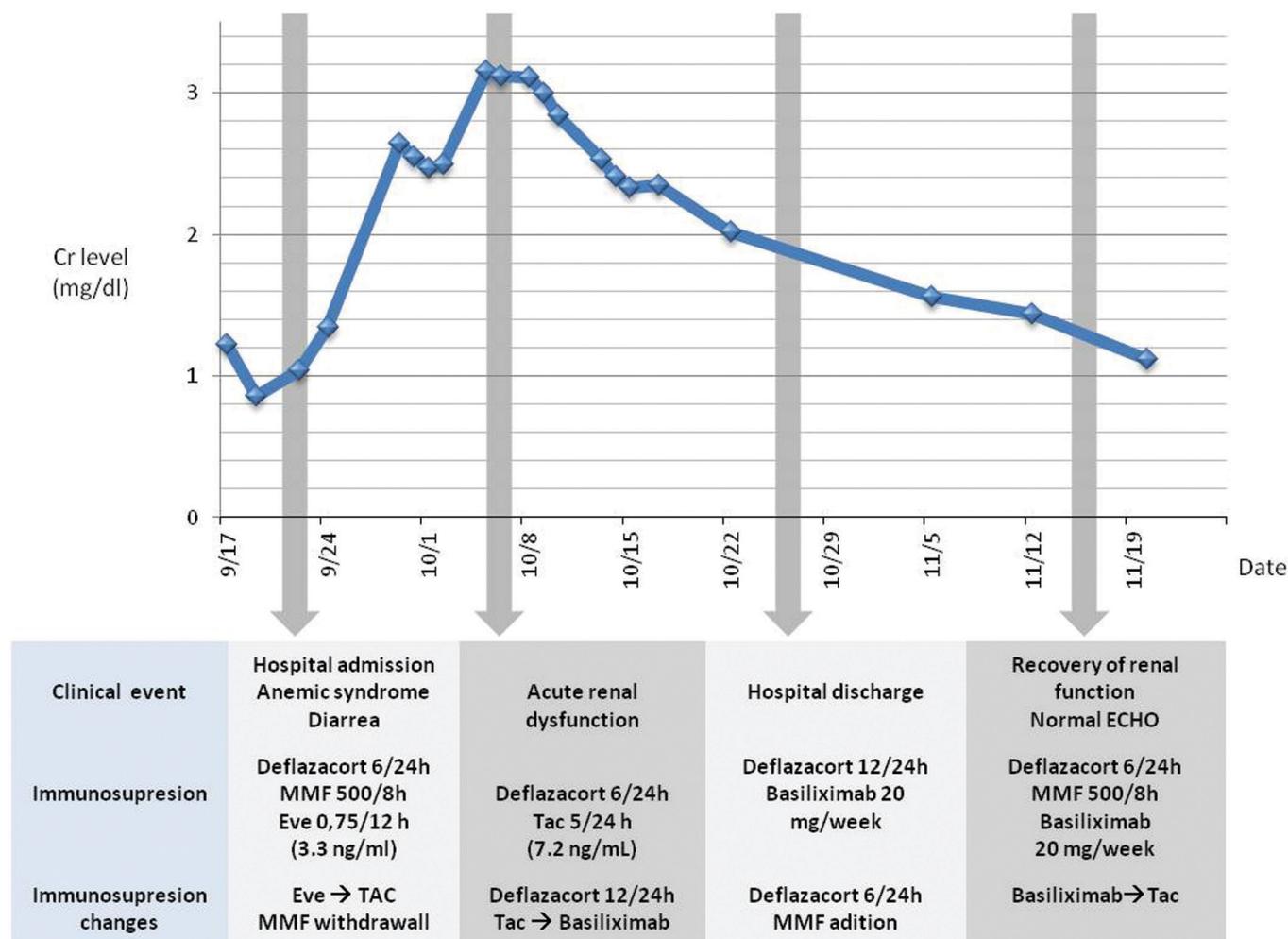
Four years later, the patient was admitted to our hospital with symptomatic severe anemia (minimal efforts dyspnea) and diarrhea for 4 days. Analytical tests showed pancytopenia

Accepted: August 1, 2014

Published online: September 1, 2014

Corresponding author:

Pau Alonso
La Fe University Hospital
Bulevar sur s/n
46008 Valencia
Valencia, Spain
pau.alonso.fernandez@gmail.com



CsA: cyclosporine; MMF: mycophenolate mofetil; Eve: everolimus; Tac: Tacrolimus; ECHO: echocardiography

Fig. 1 - Renal function parameters in patient 1 and immunosuppressive treatment.

(hemoglobin (Hb) 6.3 g/dL, leukocyte 1,300/ μ L and platelets 26,000/ μ L), a normal renal function (Cr 1.12 mg/dL) and therapeutic serum levels of immunosuppressive drugs (Eve 3.3 ng/mL). Eve and MMF were discontinued because of their myelosuppressive and toxic gastrointestinal effects. Prolonged-release Tac was started as immunosuppressive drug (5 mg/24 h, target levels 5-10 ng/mL). Deflazacort dose was also increased to 12 mg/24 h. Blood transfusions and treatment with recombinant granulocyte colony-stimulating factor were required in order to maintain hemoglobin levels above 9 g/dL, and to prevent opportunistic infections. A bone marrow biopsy was performed with the diagnosis of myelofibrosis (Jak mutation screening was negative).

Renal function at admission was preserved, with creatinine levels of 1.12 mg/dL. However, 48 hours after Tac introduction (serum levels 7.2 ng/mL) diarrhea increased and renal function worsened (Cr 3.15 mg/dL). A cardiac echocardiography showed good biventricular function without hypertrophy. It was therefore decided to temporarily suspend Tac and to replace it by weekly doses of basiliximab

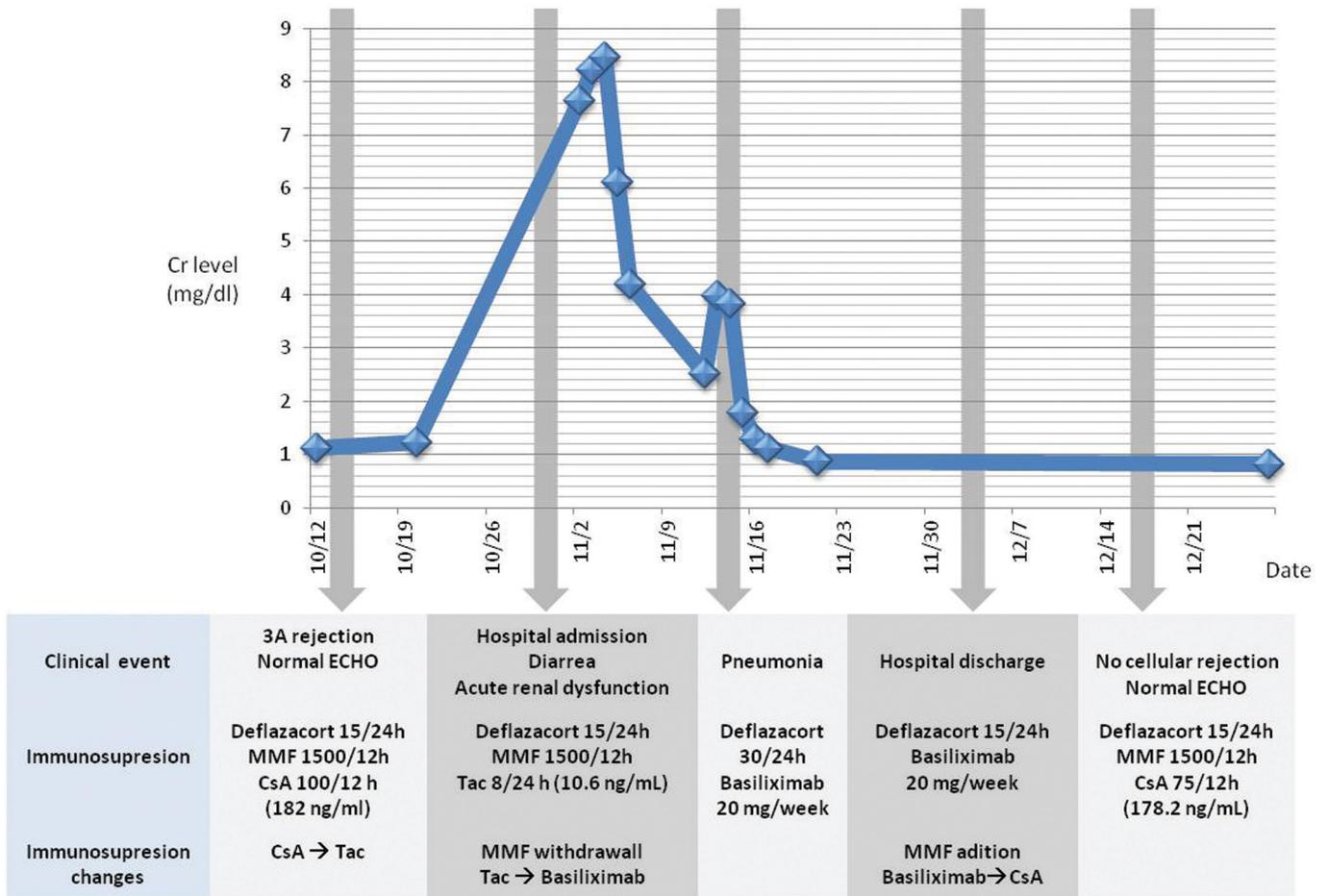
(20 mg). Renal function slowly recovered and the patient was discharged from the hospital. At discharge, creatinine serum level was 1.65 mg/dL.

After six weeks of Tac discontinuation and five ambulatory basiliximab doses, renal function recovered (Cr 1.15 mg/dL) and echocardiography results remained unchanged. Tac was successfully reintroduced. Patient required weekly blood transfusion to maintain correct Hb levels.

The development of the patient, renal function and treatment can be seen in Figure 1.

Case 2

The second case is a 55-year-old male who underwent HTx in 2011 due to a dilated cardiomyopathy. Cyclosporine A (CsA), MMF and deflazacort were used as maintenance immunosuppression. Immediate postoperative progress was not favorable, with an episode of atrial flutter and right ventricular (RV) dysfunction which required treatment with intravenous steroids. Sinus rhythm and a normal RV function



CsA: cyclosporine; MMF: mycophenolate mofetil; Tac: Tacrolimus; ECHO: echocardiography

Fig. 2 - Renal function parameters in patient 2 and immunosuppressive treatment.

were restored. Six months after HTx the patient suffered an osteoporotic vertebral fracture in relation with the steroid treatment.

Seven months after HTx a 3A grade rejection was found in the endomyocardial biopsy. RV dysfunction was found again in the echocardiographic control. Despite remaining clinically asymptomatic, the patient was treated with three methylprednisolone bolus, achieving RV function normalization at discharge.

A new 3A rejection with RV dysfunction was diagnosed in the next biopsy (ninth months) and treated again with intravenous steroids and a change in immunosuppressive drugs: CsA was replaced by prolonged-release Tac at 8 mg daily dose (target levels 10 ng/mL). At discharge, RV function was normal.

One month later, the patient was admitted in our service with persistent diarrhea, edema and dyspnea on minimal efforts. The tests showed ARD (8.62 mg/dL) and metabolic acidosis. At admission, Tac serum levels were 10.6 ng/mL. Echocardiography showed a normal left and RV function with no left ventricular hypertrophy or pericardial effusion. After removing Tac and MMF, weekly doses of basiliximab

(20 mg) were introduced as immunosuppressive therapy, and supportive therapy with intravenous fluids was established. Renal function improved with a good diuretic response and a decline in creatinine levels. The patient's progress was torpid, presenting a respiratory infection that caused a new deterioration of renal function, which was controlled with intravenous antibiotics. After 5 weeks of CNI discontinuation and four doses of basiliximab (20 mg), renal function improved, reaching normal serum creatinine levels. It was then decided to reintroduce immunosuppressive therapy with CNI, choosing CsA (75 mg/12 h, target level 100-200 ng/mL). Renal function was maintained and creatinine serum level at discharge was 1.15 mg/dL.

One month after discharge the patient was reevaluated, and blood test and endomyocardial biopsy were performed. Renal function was conserved (Cr 0.97 mg/dL) despite treatment with CsA in the therapeutic range (178 ng/mL); the biopsy showed no cellular rejection. Finally, echocardiography showed a good function of both ventricles.

The progress of the patient, renal function and treatment can be seen in Figure 2.



Discussion

ARD is a common complication during HTx follow-up and it is potentially a fatal situation. In clinical practice, there is no gold standard protocol for the management of ARD after HTx. During the early postoperative period, CNI introduction can be delayed and/or started at low doses under MAB coverage (7, 8). When ARD appears after the postoperative period, temporary CNI discontinuation with MAB coverage (CNI “holiday”) has been proved effective, allowing the reintroduction of immunosuppressive therapy when renal function is recovered (9).

CD25 is a subunit of the interleukin-2 receptor which is found exclusively on activated CD4 T lymphocytes. CD25 is crucial for clonal expansion of antiallograft host lymphocytes that mediate in acute rejection. Basiliximab is a chimeric anti-CD25 MAB commonly used to reduce the incidence of acute rejection during the induction period post-HTx. It binds to the alpha subunit on IL-2 receptor, thereby blocking the stimulation of T lymphocytes, which inhibits the host immune response against the allograft. When used in two intravenous doses of 20 mg separated by 4 days, it provides a period of 4-6 weeks of CD25 suppression. Longer use of MAB in the context of HTx patients with renal dysfunction has been reported previously. It permits the discontinuation of treatment with CNIs to allow the recovery of renal function (CNI “holiday”) either immediately after HTx or in the long term, but the experience is limited and usually close to the postoperative period of heart transplantation.

We reported our experience with daclizumab use to provide temporary discontinuation of CNI in the setting of ARD immediately after HTx (8). In these patients we used an empiric weekly dose of daclizumab. An average “holiday” of 14 days was found to be effective in normalizing renal function without increasing the rejection rate. After this period we could reintroduce the CNI treatment as usual.

Cantarovich et al have reported CNI holiday using anti-CD25 MAB in a solid organ transplant recipients’ cohort (heart and liver) (10, 11). They reported their experience using MAB in patients who required a CNI discontinuation because of ARD. Basiliximab (20 mg/dose given every 20 days) and daclizumab (1.5 mg/kg/dose given every 7 days) were successfully used. When renal function returned to baseline creatinine levels, anti-CD25 MAB therapy was interrupted and CNI was reintroduced at therapeutic doses. MABs were well tolerated in all patients, with no reported adverse events and no episodes of acute cellular rejection during the follow-up. On average, CNIs were discontinued for 21 ± 51 days (range 6-210 days) and recovery of renal function was achieved in all cases. Their results suggest that MAB therapy could be used safely and effectively in patients requiring a CNI holiday because of renal dysfunction following solid organ transplant.

In both cases, ARD seemed to be multifactorial, mainly due to the additive effect of diarrhea and immunosuppressive therapy (CNI). In situations like this it is difficult to elucidate which is the main cause of renal dysfunction (diarrhea, CNI, etc.), but it is clear that the maintenance of CNI is harmful and needs to be withdrawn. The first case shows a patient transplanted 10 years earlier with a low risk of rejection and normal echocardiographic study. He progressed favorably after

withdrawal of Tac, achieving normalization of renal function in 5 weeks that allowed the reintroduction of immunosuppression with CNI. The second case shows a younger patient, transplanted 9 months earlier, with a history of abundant cellular rejection and, therefore, with a higher risk of developing a new rejection. Four weeks after Tac withdrawal, normal renal function was achieved and reintroduction of CNIs was possible, choosing to introduce CsA. Although the rejection risk of this patient was high, the use of basiliximab was not associated with rejection, and both biopsy and echocardiography were normal.

We therefore think that in cases of ARD where CNI has to be withdrawn, the use of weekly doses of basiliximab can be an interesting option to allow CNI discontinuation until the restoration of renal function is achieved.

Disclosures

Financial support: No grants or funding have been received for this study.

Conflict of interest: None.

References

- Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. 2003;349(10):931-940.
- Alam A, Badovinac K, Ivis F, Trpeski L, Cantarovich M. The outcome of heart transplant recipients following the development of end-stage renal disease: analysis of the Canadian Organ Replacement Register (CORR). *Am J Transplant*. 2007;7(2):461-465.
- Puschett JB, Greenberg A, Holley J, McCauley J. The spectrum of cyclosporin nephrotoxicity. *Am J Nephrol*. 1990;10(4):296-309.
- Sanchez V, Delgado JF, Morales JM, et al. Chronic cyclosporine-induced nephrotoxicity in heart transplant patients: long-term benefits of treatment with mycophenolate mofetil and low-dose cyclosporine. *Transplant Proc*. 2004;36(9):2823-2825.
- Chou NK, Wang SS, Chen YS, et al. Induction immunosuppression with basiliximab in heart transplantation. *Transplant Proc*. 2008;40(8):2623-2625.
- Ortiz V, Almenar L, Martínez-Dolz L, et al. Induction therapy with daclizumab in heart transplantation—how many doses? *Transplant Proc*. 2006;38(8):2541-2543.
- Møller CH, Gustafsson F, Gluud C, Steinbrüchel DA. Interleukin-2 receptor antagonists as induction therapy after heart transplantation: systematic review with meta-analysis of randomized trials. *J Heart Lung Transplant*. 2008;27(8):835-842.
- Sánchez Lázaro I, Almenar Bonet L, Martínez Dolz L, et al. Repeated daclizumab administration to delay the introduction of calcineurin inhibitors in heart transplant patients with postoperative renal dysfunction. *Rev Esp Cardiol*. 2011;64(3):237-239.
- Anselm A, Cantarovich M, Davies R, Grenon J, Haddad H. Prolonged basiliximab use as an alternative to calcineurin inhibition to allow renal recovery late after heart transplantation. *J Heart Lung Transplant*. 2008;27(9):1043-1045.
- Cantarovich M, Metrakos P, Giannetti N, Cecere R, Barkun J, Tchervenkov J. Anti-CD25 monoclonal antibody coverage allows for calcineurin inhibitor “holiday” in solid organ transplant patients with acute renal dysfunction. *Transplantation*. 2002;73(7):1169-1172.
- Cantarovich M, Giannetti N, Routy JP, Cecere R, Barkun J. Long-term immunosuppression with anti-CD25 monoclonal antibodies in heart transplant patients with chronic kidney disease. *J Heart Lung Transplant*. 2009;28(9):912-918.