Advances of immunosuppressive therapy for heart transplantation

Katherine Lietz



Department of Cardiology, Division of Advanced Heart Failure and Heart Transplantation, University of Minnesota, Minneapolis, MN, USA

Kardiochirurgia i Torakochirurgia Polska 2005; 2 (4): 18–22

The immunosuppressive therapy after heart transplantation has undergone dramatic changes during the last decade [1, 2]. Although triple-drug therapy consisting of corticosteroids, calcineurin inhibitor and anti-proliferative agent remains the mainstem of typical immunosuppression, several new drugs were developed which showed better safety and superior anti-rejection efficacy. Almost all centers replaced azathioprine with mycophenolate mofetil for maintenance immunosuppression, nearly half of heart transplant recipients receive tacrolimus instead of cyclosporine, and an increasing number of patients are treated with, perhaps the most promising class of anti-proliferative agents, mTOR inhibitors [2, 3]. The empiric use of statin therapy, aggressive preconditioning of allosensitized recipients and the increased use of selective induction, are only few examples of changes in clinical practices that distinguished this remarkable decade of cardiac transplantation.

Anti-Proliferative Agents

The widespread use of mycophenolate mofetil (MMF) was one of the most remarkable changes that occurred during the last decade. Introduced in mid-1990s, MMF has almost completely replaced azathioprine (AZA, Imuran[®]) from maintenance immunosuppresion in nearly all heart transplant recipients in the United States (Fig. 1) [2, 3]. In 2003, seventy six percent of heart transplant recipients received MMF as part of the maintenance protocol compared to only 17% in 1995, Fig. 1.

The unique ability of MMF to selectively inhibit lymphocyte proliferation without overt bone marrow depression frequently seen in patients treated with AZA, was the first observation which led to the replacement of AZA with MMF. Two subsequent large, randomized efficacy trials comparing MMF to AZA [4, 5] showed other important advantages of MMF. The use of MMF demonstrated superior anti-rejection efficacy and improved 1- and 3-year survival, correlating with 35% reduction in mortality [3, 4]. MMF was also associated with later onset of transplant-related coronary vasculopathy (CAV) and its slower progression. Prevention of CAV development was demonstrated both in serial intravascular ultrasound studies [6], and in a large retrospective series of 26,000 HT recipients reported to UNOS [3]. The only major limitation to MMF therapy are frequent gastrointestinal side effects and opportunistic infections. A new enteric-coated form of MMF, (EC-MCS, enteric coated mycophenolate sodium, Myfortic®) was designed to reduce adverse gastrointestinal events and allow more controlled absorption, and in preliminary trials showed promising outcomes [7].

Calcineurin Inhibitors

Most of our experiences in cardiac transplantation have been based on Cyclosporine A (CsA)-based immunoprophylaxis. Its potent immunosuppressive effects result from inhibiting the transcription of IL-2 gene essential for activation and proliferation of cytotoxic T cells. Although the first oil-based formula of CsA (Sandimmune®) had a variable and unpredictable bioavailability [8], first clinical trials showed a decreased incidence and severity of rejection and improved posttransplant survival when compared to the conventional treatment with AZA and prednisone [9]. In late 1980s the oil-based formula was replaced with a new preparation, a microimulsion CsA (Neoral®). The Neoral offered better absorption, uniform bioavailability and less variability in and among patients. In a double-blind, randomized trial of 280 heart transplant recipients [10], the comparison of Sandimmune versus Neoral revealed similar six--month survival and frequency of high-grade rejection in both groups.

Author for correspondence: Katherine Lietz, M.D., PhD, Division of Cardiology, University of Minnesota, Mayo Mail Code 508, 420 Delaware Street SE, Minneapolis, Minnesota 55455, tel.: 612-626-2178, fax: 612-626-4571, e-mail: lietz020@umn.edu



Maintenance Immunosupression in the U.S. Population of Heart Transplant Recipents Years 1992-2001

Fig. 1. Maintenance immunosuppression in the U.S. population of heart transplant recipients according to the 2003 U.S. Report of the Scientific Registry of Transplant Recipients between 1992 and 2001, new drugs, such as MMF and FK506 have replaced AZA and CsA from immunosuppressive protocols at many transplant centers. The panel on the right shows the most current use of immunosuppressive drugs in heart transplant recipients was reported in 2004 by the Registry of the International Society for Heart and Lung Transplantation in 3,888 patients, who received heart transplant between January 2001 and June 2003 [1, 2]

MMF - mycophenolate mofetil; CsA - cyclosporine A; FK506 - tacrolimus; AZA - azathioprine; RAPA - rapamycin

Despite its excellent antirejection efficacy, the liberal administration of CsA has been plagued by daunting nonimmunologic adversity, including high rates of serious adverse effects, such as nephrotoxicity, neurotoxicity, hypertension, glucose and lipid metabolism disturbances, hirsuitism, and gingival hyperplasia, and frequent drug interactions [10]. Presence of many of the cardiovascular side effects may in part explain why CsA was ineffective in preventing or slowing the progression of cardiac allograft vasculopathy [11].

Since early-1990s tacrolimus (TAC, FK506, Prograf®) has been investigated as an alternative to CsA. TAC has similar mechanism of action to CsA, but is approximately 10- to 100-fold more potent. In clinical trials TAC demonstrated similar or even superior safety and anti-rejection efficacy than CsA, and had remarkably lower rates of hyperlipidemia, hypertension, gingival hyperplasia and hirsuitism [12-14]. There was also an important immunologic benefit of TAC-based therapy in high-risk heart transplant recipients, such as African Americans [15]. Since the mid-1990s TAC

has become the preferred agent in nearly half of the patients treated with calcineurin inhibitors (Fig. 1) [2, 3] and has been widely used in patients with refractory rejections receiving CsA based regimens [16, 17]. Some centers showed that TAC can also be used as monotherapy with encouraging results [18].

mTOR Inhibitors

Sirolimus (SRL, Rapamycin, Rapamune®) is one of the newest additions to immunosuppressant armamentarium introduced in 1999. SRL is an inhibitor of the mammalian target of rapamycin (mTOR) [19], the binding of which inhibits proliferative responses of lymphocytes and other cell lines that utilize mTOR signalling (endothelial cells, smooth muscle cells, fibroblasts). One of the most important properties of SRL is its ability to inhibit development of transplant-related vasculopathy. Preliminary results of a randomized trial in 136 heart transplant recipients [20] have demonstrated that in addition to effective prevention of acute rejection [21], SRL can slow progression of transplant-related vasculopathy. In a randomized study of



Induction Immunosuppression in Heart Transplant Recipents Years 2001–2003

Fig. 2. The use of induction immunosuppression in heart transplant recipients between 2001 and 2003 according to the 2005 U.S. Registry of the International Society for Heart and Lung Transplantation

46 heart transplant SRL proved to inhibit progression of CAV also in recipients with established coronary vasculopathy [22]. Development of hypercholesterolemia and hypertrigliceridemia, which is a common complications of SRL use, does not appear to affect the ability of SRL to affect progression of transplant related-coronary artery disease. The only worrisome side effect of SRL is the delay in wound healing after surgery seen in renal and liver transplantation [23, 24]. A recently published prospective, randomized multicenter trial of 334 patients showed that the combination of SRL and TAC demonstrated comparable anti-rejection efficacy at 6-months posttransplant to TAC and MMF-based protocols and may be superior to the combination of CsA and MMF [25]. The encouraging results of randomized trials with mTOR inhibitors led to increasing use of these agents as maintenance immunosuppressive drugs (Fig. 1).

Everolimus (RAD, EVL, Certican[®]) is an analogue of SRL and has a very similar mechanism of action. In a recent prospective, randomized, double-blind comparison of RAD with AZA in 634 de novo heart transplant recipients on maintenance regimen consisting of CsA and corticosteroids, 209 patients were randomized to receive low dose RAD 1.5 mg/day, 211 patients received high dose RAD 3 mg/day and 214 patients were treated with AZA 48. The results of two years follow-up revealed that the incidence of acute rejection at 6 months after transplantation and transplant-related vasculopathy at one year was significantly lower in the RAD groups than in the AZA group with the same patient survival. The optimal efficacy and safety of RAD therapy was achieved by starting RAD treatment with the dose 1.5 mg/d adjusted to target trough concentration above 3 ng/mL [26]. Mean serum creatinine concentration and lipid levels were higher in the RAD groups and led to a decrease in the CsA dose during the study.

Statins

Statins have guite unexpectedly become ancillary immunomodulatory treatment in heart transplant recipients after one-year randomized trial of 92 heart transplant recipients showed that pravastatin not only lowered cholesterol levels, but also decreased the incidence of cardiac rejection with hemodynamic compromise, improved graft survival, and lowered the incidence of coronary vasculopathy [27]. Simvastatin (10 mg/day) revealed similar beneficial effects on cardiac allograft rejection and one-year survival [28]. Therefore, it appeared that statins may have additional immunomodulatory properties aside their lipid-lowering properties. It has been suggested that the inhibition of HMG-CoA reductase enzyme by statins, may indirectly lead to a selective blockade of LFA-1-mediated adhesion and costimulation of lymphocytes, the pivotal process driving allograft rejection [19, 30]. These developments led to the inclusion of statins as part of the standard treatment in all heart transplant recipients. Unless contraindicated, all heart transplant recipients in the U.S. and many other countries should received statins as part of their immunosuppressive protocol [2, 3].



Survival by Transplantation Era after Heart Transplantation Years 1982–2003

Fig. 3. Actuarial survival after heart transplantation by transplant eras between 1982 and 2003 according to the 2005 Registry of the International Society for Heart and Lung Transplantation

Induction Therapy

The use of induction therapy after heart transplantation remains controversial. In large muti-insitutional studies, induction therapy only delayed the first rejection without reducing overall frequency and the graft survival did not improve [31]. Moreover, the incidence of often fatal infections and malignancies increased, and in patients with the lowest propensity for fatal rejection (<1.5% probability) induction therapy decreased survival by 6% [31]. With this unfavorable safety profile, only certain high-risk patients are now considered for this therapy in the United States, (Fig. 2) [2].

The mainstem of induction therapy are now humanized monoclonal antibodies, a new generation of genetically modified antibodies to resemble human antibodies [2]. The first preparations of humanized antibodies used in heart transplantation were monoclonal antibodies against the α -subunit (Tac/CD25) of interleukin-2 receptor (IL-2R), such as basiliximab or daclizumab. Induction therapy with theses agents provided more selective and non-depleting action. In randomized trials the use of daclizumab [32] and basiliximab [33] showed decreased frequency and severity of acute rejections. In addition, patients treated with selective induction were less likely to develop infections and malignancy, which are often seen with the use of non-selective agents [32]. The efficacy of daclizumab treatment appeared to directly correlate with the degree recipient and donor compatibility at the HLA-DR locus [33]. The only important limitation of these agents was that acute rejection could still occur during

treatment and when combined with previous treatment with depleting antibodies, such as OKT3, use of non-selective agents could significantly increase the risk of severe infection or sepsis [34].

Conclusions

The last decade of cardiac transplantation led to major changes in the maintenance immunosuppressive therapy used in heart transplant recipients, and the armamentarium of immunosuppressive agents available to the transplant physician is constantly growing. Defining the role of each of these agents in thoracic transplantation will still require much work and the need for pivotal trials in heart and lung transplantation is apparent. It is important to remember, however, that despite our strides to improve efficacy of immunosuppressive therapy, the long-term survival after heart transplantation has improved only minimally during the last twenty years (Fig. 3) [2, 3]. The most serious side effects of long-term immunosuppression, such as malignancy, infection and drug-induced organ failure, continue to threaten long-term survival after transplantation. Therefore, finding optimal and individualized immunosuppressive therapy will be one of the greatest challenges in the coming decade of cardiac transplantation.

References

 Taylor DO, Edwards LB, Boucek MM, Trulock EP, Keck BM, Hertz MI: The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult heart transplant report-2004. J Heart Lung Transplant 2004; 7: 796-803.

- 2. 2003 Annual Report of the U.S. Scientific Registry of Transplant Recipients and the Organ Procurement and Transplantation Network. Rockville, MD and Richmond, VA. www.ustransplant.org.
- Lietz K, Herre JM: The risk of cardiac death in heart transplant recipients with and without angiographically detected coronary vasculopathy. J Heart Lung Transplant 2005; 2: S91 [Abstract].
- 4. Kobashigawa J, Miller L, Renlund D, Mentzer R, Alderman E, Bourge R, Costanzo M, Eisen H, Dureau G, Ratkovec R, Hummel M, Ipe D, Johnson J, Keogh A, Mamelok R, Mancini D, Smart F, Valantine H: A randomized activecontrolled trial of mycophenolate mofetil in heart transplant recipients. Mycophenolate Mofetil Investigators. Transplantation. 1998; 4:507-515.
- Hosenpud JD, Bennett LE: Mycophenolate mofetil versus azathioprine in patients surviving the initial cardiac transplant hospitalization: an analysis of the Joint UNOS/ISHLT Thoracic Registry. Transplantation. 2001; 10: 1662-1665
- 6. Eisen HJ, Kobashigawa J, Keogh A, Bourge R, Renlund D, Mentzer R, Alderman E, Valantine H, Dureau G, Mancini D, Mamelok R, Gordon R, Wang W, Mehra M, Constanzo MR, Hummel M, Johnson J: Mycophenolate Mofetil Cardiac Study Investigators: Three-year results of a randomized, double-blind, controlled trial of mycophenolate mofetil versus azathioprine in cardiac transplant recipients. J Heart Lung Transplant 2005; 5: 517-525.
- 7. Kobashigawa JA, Davis SF, Renlund DG, Hummel M, Gerosa G, Grambilla R: Six month data of a 12-month, single-blind, randomized, parallel group, multicenter study to investigate the efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, myfortic[®]) compared with mycophenolate mofetil (MMF) in de novo heart transplant recipients. J Heart Lung Transplant, 2004, 2: S44-S45 [Abstract].
- Lindholm A, Kahan BD: Influence of cyclosporine pharmacokinetics, trough concentrations, and AUC monitoring on outcome after kidney transplantation. Clin Pharmacol Ther 1993, 2: 205-218.
- 9. Opelz G, Wujciak. T: The influence of HLA compatibility on graft survival after heart transplantation. N Engl J Med 1994, 12: 816-819.
- Eisen JH, Hobbs RE, Davis SF et al.: Safety, tolerability and efficacy of cyclosporine microemulsion in heart transplant recipients: a randomized, multicenter, double-blind comparison with either oil-based formulation of cyclosporine – results at six months after transplantation. Transplantation 1999, 68: 663-671.
- Gamba A, Mamprin F, Fiocchi R, Senni M, Troise G, Ferrazzi P, Ferrara R, Corbetta G: The risk of coronary artery disease after heart transplantation is increased in patients receiving low-dose cyclosporine, regardless of blood cyclosporine levels. Clin Cardiol 1997;9:767-772.
- 12. Taylor DO, Barr ML, Radovancevic B, Renlund DG, Mentzer RM Jr, Smart FW, Tolman DE, Frazier OH, Young JB, VanVeldhuisen P: A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. J Heart Lung Transplant 1999; 4: 336-345.
- Reichart B, Meiser B, Vigano M, Rinaldi M, Martinelli L, Yacoub M, Banner NR, Gandjbakhch I, Dorent R, Hetzer R, Hummel M: European Multicenter Tacrolimus (FK506) Heart Pilot Study: one-year results-European Tacrolimus Multicenter Heart Study Group. J Heart Lung Transplant 1998; 8: 775-781.
- 14. Kobashigawa JW, Miller LW, Felker GM, Russell SE, Ewald GM, Zucker M, Goldberg L, Eisen HJ, Rayburn BK, Wagoner LE, Philbin E, Pereira N, Czerska B, Kormos RL, Weston M, Conte J, Hosenpud J, Aaronson K, Hill J, Copeland JG, Czer L, Anderson A, Dec GW, Torre-Amione G, Yancy CW, Vega JD, Jarcho JA, Mancini D, Bhat G, First G, Fitzsimmons W, Tolzman D, Salm K and Gao J: 12 month report of a 3 arm multicenter comparison of Tacrolimus (TAC), MMF or TAC/Sirolimus(SRL) and steroids vs Cyclosporine microemulsion(CYA), MMF and steroids in de novo cardiac transplant recipients. J Heart Lung Transplant 2005; 2, S61-S62.
- 15. Mehra MR, Uber PA, Scott RL, Prasad AK, Park MH: Racial differences in clinical outcome using tacrolimus and mycophenolate mofetil immunosuppression in heart transplantation. Transplant Proc. 2001;1-2: 1613-1614.
- 16. Meiser BM, Uberfuhr P, Fuchs A, Schulze C, Nollert G, Mair H, Martin S, Pfeiffer M, Reichenspurner H, Kreuzer E, Reichart B: Tacrolimus: a superior agent

to OKT3 for treating cases of persistent rejection after intrathoracic transplantation. J Heart Lung Transplant 1997; 8: 795-800.

- Metzner RM Jr, Jahania MS, Lasley RD: Tacrolimus as a rescue immunosuppressant after heart and lung transplantation. US Multicenter FK506 Study Group. Transplantation 1998, 6: 109-113.
- Baran DA, Segura L, Kushwaha S, Courtney M, Correa R, Fallon JT, Cheng J, Lansman SL, Gass AL: Tacrolimus monotherapy in adult cardiac transplant recipients: intermediate-term results. J Heart Lung Transplant 2001; 1: 59-70.
- 19. Kahan BD, Camardo JS: Rapamycin: clinical results and future opportunities. Transplantation 2001 7: 1181-1193.
- 20. Keogh A: Immunosuppression: an evolving art and science. TOR inhibitors. Rapamycin: results of a randomized trial following heart transplantation. Presented at The International Society for Heart and Lung Transplantation Twenty Second Annual Meeting and Scientific Sessions; April 10-13, 2002; Washington DC.
- Kahan BD: Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. The Rapamune US Study Group. Lancet 2000; 356: 194-202.
- Mancini D, Pinney S, Burkhoff D, La Manca J, Itescu S, Burke E, Edwards N, Oz M, Marks AR: Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation 2003; 1: 48-53.
- 23. Guilbeau JM: Delayed wound healing with sirolimus after liver transplant. Ann Pharmacother 2002; 9: 1391-1395.
- 24. Valente JF, Hricik D, Weigel K, Seaman D, Knauss T, Siegel CT, Bodziak K, Schulak JA: Comparison of sirolimus vs. mycophenolate mofetil on surgical complications and wound healing in adult kidney transplantation. Am J Transplant 2003; 3: 1128-1134.
- Meiser BM, Groetzner J, Muller M: Tacrolimus and sirolimus: a new therapeutic approach for immunosuppression after heart transplantation. [Abstract] J Heart Lung Transplant. 2002; 21: 84.
- 26. Eisen HJ, Tuzcu EM, Dorent R, Kobashigawa J, Mancini D, Valantine-von Kaeppler HA, Starling RC, Sorensen K, Hummel M, Lind JM, Abeywickrama KH, Bernhardt P: RAD B253 Study Group: Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med 2003; 9: 847-856.
- Kobashigawa JA, Katznelson S, Laks H, Johnson JA, Yeatman L, Wang XM, Chia D, Terasaki PI, Sabad A, Cogert GA, et al.: Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995; 10: 621-627.
- Mehra MR, Uber PA, Vivekananthan K, Solis S, Scott RL, Park MH, Milani RV, Lavie CJ: Comparative beneficial effects of simvastatin and pravastatin on cardiac allograft rejection and survival. J Am Coll Cardiol 2002; 9: 1609-1614.
- 29. Downward J, Graves JD, Warne PH, Rayter S, Cantrell DA: Stimulation of p21ras upon T-cell activation. Nature 1990, 346: 719-723.
- Weitz-Schmidt G, Welzenbach K, Brinkmann V: Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med 2001; 6: 687-692.
- 31. Higgins R, Kirklin JK, Brown RN, Rayburn BK, Wagoner L, Oren R, Miller L, Flattery M, Bourge RC: Cardiac Transplant Research Database (CTRD): To induce or not to induce: do patients at greatest risk for fatal rejection benefit from cytolytic induction therapy? J Heart Lung Transplant. 2005; 4: 392-400.
- Beniaminovitz A, Itescu S, Lietz K, et al.: Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. N Engl J Med 2000; 9: 613-619.
- 33. Mehra MR, Zucker MJ, Wagoner L, Michler R, Boehmer J, Kovarik J, Vasquez A: A multicenter, prospective, randomized, double-blind trial of basiliximab in heart transplantation. J Heart Lung Transplant. 2005; 9: 1297-1304.
- 34. Lietz K, John R, Beniaminovitz A, Burke EM, Mancini DM, Edwards NM, Itescu S: Interleukin-2 receptor blockade in cardiac transplantation: influence of HLA-DR locus incompatibility on treatment efficacy. Transplantation 2003; 6: 781-787.
- 35. Hershberger RE, Starling RC, Eisen HJ, Bergh CH, Kormos RL, Love RB, Van Bakel A, Gordon RD, Popat R, Cockey L, Mamelok RD: Daclizumab to prevent rejection after cardiac transplantation. N Engl J Med 2005 30; 26: 2705-2713.