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# Immunosuppression in cardiac transplantation: state of the art and new drugs

Stephan Korom

## Summary

Although the contemporary armamentarium of immunosuppressive drugs in cardiac transplantation has reduced the incidence and severity of acute rejection, their associated toxicities represent major obstacles to long-term use. A score of new immunosuppressive agents for use in transplantation medicine have entered clinical trials. Three small molecules, targeting intracellular pathways (ISA247, a semisynthetic cyclosporine analogue; AEB071, a protein kinase C inhibitor; CP 690550, a Janus kinase 3 inhibitor), and three biologics, immunoglobulins interfering with lymphocyte surface receptor signalling (belatacept, an improved CTLA4Ig; efalizumab, an anti-LFA1-antibody; alefacept, an LFA3-IgG1 fusion receptor protein), are currently being assessed in phase II/III trials.

*Key words: cardiac transplantation; immunosuppression; new immunosuppressive drugs*

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## Introduction

During the four decades since the first successful cardiac transplantation by Barnard [1], >80,000 patients worldwide [2] have been engrafted, demonstrating in remarkable fashion the incorporation of this complex procedure into clinical practice. Transplant half-life is at ten years, approaching thirteen years for recipients surviving the first twelve months [2]. The current state of clinical heart transplantation reflects advances in a large number of associated areas, most notably in the fields of anti-infectious and immunosuppressive therapy. As in other domains of solid organ transplantation, the

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**Table 1**

Currently employed immunosuppressive drugs in cardiac transplantation.

Immunosuppressive class	Mode of action	Comment
Polyclonal antilymphocyte antibody preparations (equine, ATGAM; rabbit, thymoglobulin).	Substantial lymphocyte depletion.	Decreasing role for induction therapy. Risk of allergic reaction, cytokine release syndrome.
Monoclonal antilymphocyte antibody preparation (mouse, OKT3).	Binds to CD3 (as part of the TCR), blocking T-cell activation and leading to lymphocyte depletion.	Rarely used for induction. Cytokine release syndrome.
Anticytokine receptor antibodies (humanised, daclizumab; chimeric, basilixumab).	Non-depleting anti-IL-2R (CD25) antibodies.	Low rate of adverse events. Most commonly used induction agents.
Campath-1H (alemtuzumab).	Humanised monoclonal anti-CD52 antibody, inducing complement- and antibody-dependent T-cell lysis.	Experience with this antibody in induction therapy is still limited.
Corticosteroids (prednisone, prednisolone, methylprednisolone).	Extensive transcriptional regulation (inhibition of activator protein-1 and NF $\kappa$ -B) in lymphocytes and non-immune cells, inducing immunosuppressive and anti-inflammatory effects.	Standard component of induction, maintenance and anti-rejection therapy.
Calcineurin inhibitors (CNI; cyclosporine A, tacrolimus).	Transcription-inhibition of key-cytokines (IL-2, -4, IFN- $\gamma$ , TNF- $\alpha$ ).	In spite of major side effects (nephrotoxicity, diabetogenicity, neurotoxicity, lipid disorders, hypertension), CNI remain a cornerstone in cardiac transplantation.
Antimetabolites (azathioprine, mycophenolic acid).	Purine-synthesis blockers, targeting proliferating lymphocytes.	Mycophenolic acid has replaced azathioprine due to lower toxicity and possibly better efficacy. Together with CNI, antimetabolites form the backbone of immuno-suppressive therapy in lung transplantation.
mTOR inhibitors (sirolimus, everolimus).	Blocking G1-to-S-phase cell cycle progression, targeting proliferating lymphocytes and non-haematopoietic cells (e.g., smooth muscle cells).	Most recent immunosuppressive agents with the potential to decrease the burden of CNI-nephrotoxicity and CAV. However, their distinctly adverse event profile limits their de novo use.

focus has shifted from treating acute rejection episodes to ameliorating side effects of contemporary immunosuppressants and late causes of graft failure. Several novel immunosuppressive drugs with the potential to address previously unmet medical needs in transplant recipients have entered clinical trials (table 1). In this review, the up-to-date immunosuppressive standard of care is summarised, novel concepts and trials with approved drugs are discussed and new compounds in clinical studies are introduced.

### Immunosuppression in cardiac transplantation: state of the art

Induction therapy with antilymphocyte antibodies is currently employed in 51% of recipients, primarily using non-depleting IL-2 receptor antibodies (IL-2RA) (28%), alongside anti-thymocyte globulin (ATG) (20%) and OKT3 (<3%) [2]. Calcineurin inhibitors (CNI) are still the cornerstone of immunosuppression (IS) in maintenance therapy, with tacrolimus being more frequently used than cyclosporine (57% vs 37%). At most centres CNI are combined with an antimetabolite

agent, where mycophenolate mofetil (MMF) is the current standard of care (77%) [2]. Alternatively, a proliferation signal inhibitor (PSI/mTOR inhibitor) such as rapamycin (sirolimus) may be given (13%) [2]. Triple-drug immunosuppressive therapy is supplemented – at least during the first year after transplantation – by the addition of a corticosteroid (CS) (63%) [2]. Historically, success of cardiac transplantation has been defined by the abrogation of rejection sequences, and even today, following the first month until the end of the first year, acute rejection (AR) accounts for 12% of all deaths [2]. Classically, antirejection treatment rests upon the use of CS-, antilymphocytic-, and anti-cytokine-receptor therapy, and may be supported by modifications in the maintenance immunosuppressive regimen (e.g., withholding steroid taper, switch in CNI, conversion to a proliferation-signal-inhibitor-based regimen, etc.), often designed to interrupt a recurrent or refractory pattern of a given rejection situation [3]. There are only ten listed ongoing trials assessing the use of pharmacological immunosuppressants in adult cardiac transplantation (table 2).

**Table 2**  
Ongoing trials assessing the use of pharmacological immunosuppressants in adult cardiac transplantation. (Searched under <http://clinicaltrials.gov/> and <http://www.anzctr.org.au/default.aspx>, as of November 2008).

Purpose/Title/ Identification number	Primary endpoint	Design	Sponsor	Participants	Enrolment	Completion
COREV: A multicentre, randomised, open-label study evaluating the efficacy on renal function of everolimus in heart transplantate recipients with established chronic renal failure. NCT00716573	Evaluation of renal function at 12 months after everolimus introduction and decrease in doses of anticalcineurin.	Randomised, multi-centre, open-label.	Hospices Civils de Leon, Spain	Hospices Civils de Leon, Spain	?	Not yet recruiting
Assessment of gastrointestinal tolerability and efficacy of enteric-coated mycophenolate sodium (Myfortic®) in heart transplant recipients. NCT 00574197	Side effects using the GRS (Gastro-intestinal symptoms rating scale), GI complications and GI adverse events at 6 months.	Non-randomised, open-label, uncontrolled, single-group.	Cedars-Sinai Medical Center, USA Novartis	Cedars-Sinai Medical Center, USA	20	01/2009
Open-label, randomised study comparing the Patient Reported Severity of GI side effects, of MMF versus EC-MPS in maintenance heart transplant patients. NCT00468936	Reduction in GRS (gastrointestinal symptoms rating score) at 6 months.	Randomised, open-label, single-centre.	McGill University Health Center, Canada Novartis	McGill University Health Center, Canada	?	12/2009
Pharmacokinetics of MMF alone and in combination with valganciclovir in renal and heart transplant recipients. NCT00189150	To determine whether a clinically significant pharmacokinetic drug interaction exists between MMF and valganciclovir under steady state conditions in renal and heart transplant recipients.	Non-randomised, open-label, active control, single group assessment, pharmacokinetics study.	University of Michigan, USA Roche	University of Michigan, USA	24	?
A 24-month, multi-centre, randomised, open-label, non-inferiority study of efficacy and safety comparing two exposures of concentration-controlled everolimus with reduced cyclosporine vs 3.0g MMF with standard dose cyclosporine in in de novo heart transplantation. NCT00300274	Biopsy-proven acute rejection episodes associated with haemodynamic compromise, graft loss/retransplant, death or loss to follow-up at 12 months.	Randomised, multi-centre, open-label, dose comparison, parallel assignment.	Novartis	International	630	?
Randomised, open-label study to compare the safety and conversion from a calcineurin efficacy of inhibitor in heart transplant recipients with mild to moderately impaired renal function. NCT00369382	Calculated change from baseline of creatinine clearance (using Cockcroft-Gault equation) at 52 weeks.	Randomised, multi-centre, open-label, active control, parallel assignment, efficacy study.	Wyeth	International	200	04/2009
TICTAC: Prospective, randomised open-label study in de novo cardiac transplant recipients, exploring tacrolimus plus MMF with rapid steroid weaning vs. tacrolimus monotherapy after 2 wk MMF therapy plus rapid steroid weaning at 12 months. NCT00299221	ISHLT biopsy score at 6 and 12 months.	Randomised, open-label, parallel assignment, efficacy.	Astellas	Newark, Beth Israel Medical Center, USA	150	06/2009
EVEROSTAT: Prospective and randomised study to evaluate the effect of everolimus in the clinical and intracardiac ecography progression of heart graft vascular illness. NCT00695344	Percentage of patients presenting at least one major clinical event due to graft vascular illness during the first year of the study on both treatment arms.	Randomised, open-label, active control, parallel assignment, safety/efficacy study.	Hospital Puerta de Hierro, Spain	Multi-centre, Spain	104	06/2010
Effect of everolimus and CNI minimisation on renal function. NCT00596557	Evolution of renal function after initiation of everolimus and minimalisation of CNI dose.	Prevention, non-randomised, open-label, active control, parallel assignment, safety/efficacy study.	Rabin Medical Center, Israel	Rabin Medical Center, Israel	20	02/2009
NOCTET: Nordic certican trial in heart and lung transplantation. NCT00377962	Assessment and comparison of renal function by measured GFR between treatment groups, using the change from baseline to month 12 treatment.	Prevention, randomised, open-label, active control, parallel assignment, safety/efficacy study.	Novartis	Multi-centre, Scandinavia	300	?

## Corticosteroid withdrawal and CNI minimisation

Corticosteroids are the major contributor to additional bone loss following transplantation, 28% of recipients being diagnosed with lumbar osteoporosis and up to 30% sustaining vertebral compression fractures [4]. New onset diabetes (NODM) occurs in 32% of cardiac allograft recipients, and glucose intolerance has been associated with increased severity of cardiac allograft vasculopathy (CAV) [4, 5]. Due to these significant side effects, many centres try to eliminate CS as part of their maintenance immunosuppressive regimen. As reflected in the annual ISHLT reports, from 2004 to 2008, CS discontinuation increased from 20% to 37% of patients at one year post transplantation respectively [2, 6]. Early (within the first month) and late (by months 6–12) withdrawal of CS are the two most often practised approaches, with success rates ranging from 48–70% (early) to 80% (late) [7].

Four years after cardiac transplantation up to 40% of patients suffer from chronic renal failure (CKF) [8], with CKF itself increasing the relative risk of death more than fourfold, compared to recipients of non-renal transplants without CKF [9]. Since CNI-associated nephrotoxicity is responsible for deterioration of kidney function, great efforts have been directed towards minimising or even eliminating this class of drugs from maintenance immunosuppressive therapy. However, at the one-year mark only 7% of recipients have achieved a CNI-free protocol [2]. Altogether, the bulk of studies aiming to reduce/eliminate CNI hinge on the employment of a PSI/mTOR inhibitor, using the class's lack of nephrotoxicity and synergistic mode of action (to CNI). Complete *de novo* CNI avoidance has only been described in ten recipients up to now, using rapamycin, MMF, CS and induction therapy. Efficacy and tolerability over twelve months were acceptable, but the course was complicated by side effects [10, 11]. CNI minimisation in the past has been reported on the basis of a switch from azathioprine to MMF [12]. Contemporary CNI-minimisation studies in cardiac Tx rely on the superior efficacy of PSI/mTOR inhibitors and the existing synergism between the two classes. Both with sirolimus [13] and everolimus [14], CNI were successfully reduced in *de novo* cardiac Tx, achieving reduction and/or preservation of pretransplant serum creatinine. Finally, CNI elimination in maintenance patients with severe renal impairment has attracted great interest in the community, since it may offer an alternative to impending dialysis. Since 2002 [15], some 15 mostly single centre trials of replacement of CNI by either sirolimus or everolimus have been reported [12]. Although renal function was preserved or improved in most of the patients switched from CNI to PSI/mTOR inhibitors, some patients did not benefit from the changeover [16, 17]. Accumulating evidence suggests that improvement in kidney function will correlate with time after transplantation and the renal reserve (as measured by pre-switch creatinine clearance) [17].

## New immunosuppressive drugs in solid organ transplantation

During the last decade no new class of immunosuppressive drug has been approved for transplantation. However, several compounds – small molecules (non-protein drugs) and biological agents – have entered clinical trials. ISA247 (novel CNI), AEB071 (protein kinase C inhibitor) and CP 690,550 (Janus kinase inhibitor) are small molecules, currently in phase II clinical studies, and the biological agents belatacept (CTLA4Ig), efalizumab (anti-LFA1) and alefacept (LFA-3-IgG1 fusion protein) are in phase II/III [18]. With AR having become more controllable in recent years, these newer drugs hold the promise of fewer toxicities and an improved long-term outcome.

### Small molecules

ISA247 (Isotechnika) is a semisynthetic CNI which has shown higher immunosuppressive efficacy than cyclosporine, with less nephrotoxicity [19]. In a 6-month phase II trial enrolling 334 *de novo* renal transplant recipients, the efficacy and safety of ISA247 were compared with tacrolimus, in combination with MMF and an IL-2RA [20]. With similar efficacy and renal function, but a lower incidence of new onset diabetes versus tacrolimus, ISA247 may enter phase III testing.

Inhibiting protein kinase C isoforms, AEB071 (Novartis) targets a novel T cell activation pathway, with minimal impact on nuclear factor of activated T cells (NFAT) or cytokine/growth factor-mediated cell proliferation [21, 22]. With a distinct mode of action, AEB may lack nephrotoxicity and other CNI-associated side effects. Two phase II trials in *de novo* renal transplantation assessing AEB were stopped due to increased acute rejection [18]: a CNI withdrawal study (tacrolimus/AEB for three months, followed by replacement of tacrolimus with mycophenolic sodium [MPS]) and a CNI-free regimen (AEB/MPS). A third study is ongoing, evaluating an AEB/everolimus versus AEB/tacrolimus regimen, both with steroids, also in *de novo* kidney transplanted patients.

Janus kinases (JAK) are cytoplasmic tyrosine kinases which are involved in cell surface receptor signalling pathways, predominantly with members of the cytokine receptor common gamma chain family [23]. Of a group of four JAK, JAK3 appears the most promising target since its expression is restricted to haematopoietic cells, and the absence of JAK3 has been associated with severe immunodeficiency [18]. *De novo* treatment of renal transplant recipients with the JAK3 inhibitor CP 690,550 (Pfizer) versus tacrolimus in combination with an IL-2Ra, MMF and CS has shown comparable results for biopsy-proven acute rejection and renal function at six months [18].

## Biological agents

Costimulatory blockade, especially targeting the CD28/B7 pathway, has been at the centre of intensive research during the last decade. Belatacept (Bristol-Myers-Squibb) is a fusion protein, linking a human Fc fragment to CTLA-4 (cytotoxic T-lymphocyte antigen-4, CD152). It constitutes a competitive antagonist for CD28, effectively blocking interaction with CD80/86 and thus inhibiting signal 2 [18]. Belatacept is currently employed in three phase II trials in de novo kidney transplantation: one study in recipients receiving grafts from extended criteria donors, another enrolling patients engrafted with kidneys from living or standard criteria donors, and a rapid steroid withdrawal trial [18]. Furthermore, a maintenance study, investigating conversion from CNI to belatacept, a liver transplant study, and a trial for induction of tolerance (supported by the Immune Tolerance Network, <http://www.immunetolerance.org/professionals>) are underway.

Efalizumab (Genentech) is an anti-adhesion molecule consisting of a CD11a-specific IgG1, initially developed and approved for psoriasis. In a phase II study in renal transplantation with high dose (2 mg/kg) efalizumab and standard dose cyclosporine, higher incidences of posttransplant lymphoproliferative disease (PTLD) were observed [24]. Similarly to efalizumab, alefacept (Astellas) also targets lymphocyte adhesion as a human LFA-3-IgG1 fusion protein [25]. Approved for the indication of psoriasis as well, alefacept has been shown to selectively reduce T memory cells, which are pivotal in maintaining therapy-resistant/recurrent states of rejection [26]. Currently a phase II randomised multicentre study is in progress to assess the safety and efficacy of maintenance therapy in kidney allograft recipients [25].

## Conclusion

A host of new compounds which promise to modify the alloimmune response are currently being investigated in preclinical and clinical trials. Novel concepts and targets expanding the horizon of conventional immunosuppression are likely to emerge. Initially driven by the larger field of kidney transplantation, the heart transplantation community may derive major benefit from these innovations. However, active participation in both local trials and registration studies is needed to further develop and adapt these immunosuppressive regimens to cardiac transplantation.

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