Effects of immunosuppressive agents on neutrophils inflammatory response in humans: an inflammatory perspective on coronary allograft vasculopathy

Diana Chaar¹,², Martin G. Sirois¹,³, Michel White¹,²

¹Research Center, Montreal Heart Institute, Montréal, H1T 1C8, Canada
²Departments of Medicine, Faculty of Medicine, Université de Montréal, Montréal, H3T 1J4, Canada
³Departments of Pharmacology, Faculty of Medicine, Université de Montréal, Montréal, H3T 1J4, Canada

Correspondence: Michel White
E-mail: m_white@icm-mhi.com
Received: January 08, 2016
Published online: March 08, 2016

Cardiac transplantation (CTx) has improved survival in patients with advanced heart failure. Unfortunately, the conditional survival remains less than 15 years. The primary cause of mortality at 5 years following a CTx is the development of accelerated coronary atherosclerosis named coronary allograft vasculopathy (CAV). The neutrophils likely play an important role in this diffuse inflammatory process. Nevertheless, the contribution of the neutrophils on the pathogenesis of CAV is poorly understood. Regardless of their essential contribution for the prevention of graft rejection, immunosuppressive drugs (IDs) may have detrimental effects via some pro-inflammatory activities. This review presents the role of neutrophils on vascular inflammation and on the biologic effects of diverse immunosuppressive agents including mTOR inhibitors in the context of the pathophysiology of CAV. We investigated the impact of different IDs on the inflammatory responses of isolated human neutrophils harvested from healthy controls and herein, we reported on some novel characteristics of everolimus (EVE) on isolated neutrophils in comparison with other immunosuppressive agents. These biologic effects may contribute to their beneficial effects on the allograft vasculature and consequently on the prevention of CAV.

Keywords: immunology; immunosuppressive drugs; inflammation; neutrophils


Copyright: © 2016 The Authors. Licensed under a Creative Commons Attribution 4.0 International License which allows users including authors of articles to copy and redistribute the material in any medium or format, in addition to remix, transform, and build upon the material for any purpose, even commercially, as long as the author and original source are properly cited or credited.

The pathogenesis of CAV: an inflammatory perspective

CAV is a major cause of long-term mortality following heart transplantation [1-10]. CAV may affect up to 50% of patients 5 years after transplantation [11]. Compared with atherosclerotic coronary artery disease, CAV is characterized by diffuse, concentric and progressive intimal hyperplasia of the graft arteries affecting both the epicardic and the intramyocardial vessels [11, 12]. Intimal hyperplasia results from the proliferation and migration of vascular cells, particularly smooth muscle cells (SMC), which leads to a progressive and irreversible obstruction of the arteries and finally to chronic
The immunologic milieu appears to play a significant role on this pathological state [5]. The coronary artery endothelial cells from the donor, express major histocompatibility complex (MHC) class I and II antigens which appear to be primary targets of the cell-mediated and humoral immune responses [5]. These antigens are thought to be recognized by recipient CD8+ and CD4+ T cells, leading to their activation and cytokines secretion (interleukins, interferons, and tumor necrosis factors), which promote proliferation and further activation of alloreactive T cells, monocytes, and macrophages [15]. Macrophages are then recruited to the intima where they release cytokines (IL-1; IL-6; TNF-alpha) and growth factors (platelet derived growth factors (PDGF), transforming growth factor-alpha (TGF-alpha), and TGF-beta1), inducing SMC proliferation and synthesis of extracellular matrix [16]. T cells activation also stimulates the expression of adhesion molecules (intercellular cell adhesion molecule -1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), P-selectin thereby activating endothelial cells, enabling recruitment of neutrophils and the development of CAV [11, 17-23]. Indeed most pro-inflammatory markers are elevated early and late following CTx [5, 24]. Taken together, these data strongly suggest that transplantation is a significant pro-inflammatory condition.

Neutrophils are the most abundant type of white blood cells and are known to play important roles in inflammation [25-27]. Because neutrophils are able to release numerous mediators, including pro-inflammatory (IL-1α/β; -6; -7; -8; -9; -16), pro-inflammatory/angiogenic (tumor growth factor TGF-α; vascular endothelial growth factor VEGF), and anti-inflammatory mediators (IL-1 receptor antagonist (IL-1RA), TGF-β), they likely play a pivotal yet not well characterized role in the initiation and the development of CAV [28]. Previous studies have demonstrated the potential deleterious role of neutrophils during myocardial reperfusion immediately after CTx in rodents, notably via neutrophil activated αMβ2 integrin complexes (CD11b/CD18) [29, 30]. These studies reported that β2 integrin mediated neutrophil infiltration and accumulation in the cardiac allograft tissue was associated with acute rejection in mice. Neutrophils are associated with ischemia reperfusion (IR) injury [31]. They are recruited to transplanted organs by the inflammatory chemokine secreted by the graft vasculature, such as TNF-α and IL-1 [32].

King et al. further studied the role of neutrophils in the development of CAV in a mouse model. In this study, aortic transplants were performed in the presence of therapeutic levels of cyclosporine A and subsequently aortas were harvested at different times after transplantation. These investigators demonstrated that allografts harvested 1 day post-transplant exhibit > 90% loss of smooth muscle cells (SMC), and this loss of SMC was correlated with neutrophil count. Interestingly, by depleting neutrophils from recipients (using anti-PMN serum), they showed that SMC loss was significantly reduced. These results provide evidence that the neutrophils are responsible for the SMC remodeling and more specifically early SMC loss in allograft model. Interestingly, King et al. provided evidence for activation of early innate events by IR contributes to the mechanism involved in the onset of CAV. However, the role of early SMC loss in the pathophysiology of CAV is unclear since the onset of CAV is more complex than a simple correlation with SMC loss. The same investigator reported that SMC loss was biphasic with an early (1 day and 1 week) but also late loss following CTx (5-8 weeks) [32]. Interestingly, it has been shown that the late SMC loss post-transplant, likely due to adaptive immunity, is linked to further neointimal lesion formation [32, 33].

**Impact of immunosuppressive regimens on CAV**

The commonly used immunosuppressive drugs (IDs) following CTx include calcineurin inhibitors (CNIs), mTOR inhibitors, mycophenolate agents and corticoids [34, 35]. In addition to their ability to prevent allograft rejection, the IDs have distinct impact on the cardiac intrinsic characteristics as well as on the development of pro-inflammatory conditions such as diabetes, hyperlipidemia and hypertension.

Calcineurin inhibitors (CNIs): Upon entry in the T-cell, cyclosporin A (CsA) and tacrolimus (TAC) modulate their effect by binding to cytosolic proteins named the immunophilins. CsA forms a high affinity complex with cyclophilin while TAC binds with high affinity to the FK binding protein. The association between the drug and immunophilins affects T-cell activation [36] by inhibiting calcineurin, which leads to the inhibition of the calcium-calcineurin pathway, a rate-limiting step in T-cell activation. In addition, TAC and CsA inhibit the activation of MAPKinases and transcription factors, and decrease apoptosis in cardiomyocytes, vascular cells, thereby affecting cardiovascular remodeling and vasculopathy [24, 37-40]. CNIs are well known as the cornerstone of IDs for CTx recipients.

graft rejection and graft loss [11, 12]. The development of CAV is related to some immune/inflammatory mechanisms [13, 14], and traditional risk factors [2] resulting in a pro-inflammatory milieu. Immunologic and transplant related mechanisms include donor age, HLA mismatches, rejections, and selected infections such as cytomegalovirus. Non-immune mechanisms implicated in the development of CAV include traditional risk factors such as hypertension, dyslipidemia, metabolic syndrome, diabetes, obesity, and smoking [3].

The immunologic milieu appears to play a significant role on this pathological state [5]. The coronary artery endothelial cells from the donor, express major histocompatibility complex (MHC) class I and II antigens which appear to be primary targets of the cell-mediated and humoral immune responses [5]. These antigens are thought to be recognized by recipient CD8+ and CD4+ T cells, leading to their activation and cytokines secretion (interleukins, interferons, and tumor necrosis factors), which promote proliferation and further activation of alloreactive T cells, monocytes, and macrophages [15]. Macrophages are then recruited to the intima where they release cytokines (IL-1; IL-6; TNF-alpha) and growth factors (platelet derived growth factors (PDGF), transforming growth factor-alpha (TGF-alpha), and TGF-beta1), inducing SMC proliferation and synthesis of extracellular matrix [16]. T cells activation also stimulates the expression of adhesion molecules (intercellular cell adhesion molecule -1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), P-selectin thereby activating endothelial cells, enabling recruitment of neutrophils and the development of CAV [11, 17-23]. Indeed most pro-inflammatory markers are elevated early and late following CTx [5, 24]. Taken together, these data strongly suggest that transplantation is a significant pro-inflammatory condition.

Neutrophils are the most abundant type of white blood cells and are known to play important roles in inflammation [25-27]. Because neutrophils are able to release numerous mediators, including pro-inflammatory (IL-1α/β; -6; -7; -8; -9; -16), pro-inflammatory/angiogenic (tumor growth factor TGF-α; vascular endothelial growth factor VEGF), and anti-inflammatory mediators (IL-1 receptor antagonist (IL-1RA), TGF-β), they likely play a pivotal yet not well characterized role in the initiation and the development of CAV [28]. Previous studies have demonstrated the potential deleterious role of neutrophils during myocardial reperfusion immediately after CTx in rodents, notably via neutrophil activated αMβ2 integrin complexes (CD11b/CD18) [29, 30]. These studies reported that β2 integrin mediated neutrophil infiltration and accumulation in the cardiac allograft tissue was associated with acute rejection in mice. Neutrophils are associated with ischemia reperfusion (IR) injury [31]. They are recruited to transplanted organs by the inflammatory chemokine secreted by the graft vasculature, such as TNF-α and IL-1 [32].

King et al. further studied the role of neutrophils in the development of CAV in a mouse model. In this study, aortic transplants were performed in the presence of therapeutic levels of cyclosporine A and subsequently aortas were harvested at different times after transplantation. These investigators demonstrated that allografts harvested 1 day post-transplant exhibit > 90% loss of smooth muscle cells (SMC), and this loss of SMC was correlated with neutrophil count. Interestingly, by depleting neutrophils from recipients (using anti-PMN serum), they showed that SMC loss was significantly reduced. These results provide evidence that the neutrophils are responsible for the SMC remodeling and more specifically early SMC loss in allograft model. Interestingly, King et al. provided evidence for activation of early innate events by IR contributes to the mechanism involved in the onset of CAV. However, the role of early SMC loss in the pathophysiology of CAV is unclear since the onset of CAV is more complex than a simple correlation with SMC loss. The same investigator reported that SMC loss was biphasic with an early (1 day and 1 week) but also late loss following CTx (5-8 weeks) [32]. Interestingly, it has been shown that the late SMC loss post-transplant, likely due to adaptive immunity, is linked to further neointimal lesion formation [32, 33].

**Impact of immunosuppressive regimens on CAV**

The commonly used immunosuppressive drugs (IDs) following CTx include calcineurin inhibitors (CNIs), mTOR inhibitors, mycophenolate agents and corticoids [34, 35]. In addition to their ability to prevent allograft rejection, the IDs have distinct impact on the cardiac intrinsic characteristics as well as on the development of pro-inflammatory conditions such as diabetes, hyperlipidemia and hypertension.

Calcineurin inhibitors (CNIs): Upon entry in the T-cell, cyclosporin A (CsA) and tacrolimus (TAC) modulate their effect by binding to cytosolic proteins named the immunophilins. CsA forms a high affinity complex with cyclophilin while TAC binds with high affinity to the FK binding protein. The association between the drug and immunophilins affects T-cell activation [36] by inhibiting calcineurin, which leads to the inhibition of the calcium-calcineurin pathway, a rate-limiting step in T-cell activation. In addition, TAC and CsA inhibit the activation of MAPKinases and transcription factors, and decrease apoptosis in cardiomyocytes, vascular cells, thereby affecting cardiovascular remodeling and vasculopathy [24, 37-40]. CNIs are well known as the cornerstone of IDs for CTx recipients.
Nevertheless, they also contribute to the morbidity following CTx [41].

Many IDs such as CNIs have been shown to exhibit side effects, which lead to the increase of cholesterol and triglycerides [47, 48]. Hyperlipidemia is involved in the pathogenesis of CAV [48]. In comparison with CsA, TAC exhibits a smaller impact on lipid profile but a similar effect on the development of CAV. It was shown, in a randomized trial, that patients treated with TAC and mycophenolate mofetil (MMF) had significantly lower serum triglyceride levels than those who were treated with CsA and MMF [45]. Therefore, the use of TAC combined with MMF has been shown to result in better outcomes which is partly related with a lower rate of CAV in small and large clinical trials [45,46]. In addition to their lipid lowering activity, statins may reduce the progression of CAV [49-52]. The mechanisms involved with such beneficial effects remain largely unknown but likely involve anti-inflammatory and immunosuppressive effect [2, 13, 50, 52-54]. In fact, pravastatin decrease the levels of C-reactive proteins in CTx recipients [50]. Patients treated with both pravastatin and simvastatin showed a decrease in the incidence of CAV but also yielded a significant beneficial impact on survival post-CTx [56, 55].

Independently on their effects on the morbid conditions outlined above, CNIs are associated with direct reversible and irreversible nephrotoxic effects [56]. There are likely many mechanisms involved with some of which remain not fully understood. These mechanisms include renal and systemic vasoconstriction, increased endothelin-1 levels, decreased production of nitric oxide and an increased expression of TGF-beta [56-59]. Also, CsA reduces the activity of lipoprotein lipase and inhibit prednisone clearance upon interaction with cytochrome P-450 [60].

Despite their potent IDs effects, CNIs caused coronary endothelial dysfunction due to their direct toxic effects on the vascular endothelium. Indeed while CNIs can prevent acute rejection very effectively, they do not seem to have any significant effect on the prevention of CAV [10], indicating that CAV is mediated via some pathways not modulated via the calcineurin pathway.

Badiwala et al. [61] demonstrated that CsA induces injuries by increasing ICAM-1 expression on human coronary artery endothelial cells, thus promoting neutrophil adhesion. This effect could ultimately increase local cardiac inflammation and consequently facilitate the development of CAV. Although the function and effect of CNI-induced endothelial dysfunction in the pathogenesis of CAV is poorly understood, it has been demonstrated that both CsA and TAC induce vascular oxidative stress, increased endothelin-1 (ET-1) release, and contribute to the dysregulation of endothelial nitric oxide synthase (NOS) in the kidney [44, 62-64]. Indeed CNI-induced endothelial dysfunction includes the attenuation of the endothelium to release NO [65], a physiologically relevant mechanism because decreased NO bioavailability is related to the production of reactive oxygen species (ROS) and thus oxidative stress [65].

The effects of CsA and TAC exhibit some biologic differences on the arterial vasculature. The difference between CsA and TAC was further evaluated in an in vitro study analyzing the prostaglandin I2 (PGI2) and ET-1 on microvascular capillaries [87]. In this study, CsA caused some detrimental effects on capillary morphology and resulted in a significant increase in capillary ET-1 release, while TAC did not [66]. Furthermore, CsA yielded a greater impairment in brachial endothelial function using high resolution vascular ultrasound in renal transplant patients, compared with TAC treated patients [67]. Additionally, in another clinical study comparing the effects of both CNIs on endothelial function, ET-1 levels and vascular remodeling in CTx patients, the investigators reported that microvascular endothelial function was worst, concomitantly with higher ET-1 plasma levels, and a larger increase in coronary intimal area in CsA-treated patients [65]. Hence, it appears that despite some controversial observations, TAC may be less harmful than CsA on the arterial vasculature including microvascular, endothelial function, intimal thickening and arterial vascular remodeling [65].

**mTOR and mTOR inhibitors**

The inhibitors of the mammalian target of rapamycin (mTOR) are an important and unique class of immunosuppressive agents. mTOR is known to have two major functions: the activation of p70S6 kinase and the activation of the eukaryotic initiation factor 4E (eIF-4E)-phosphorylatable heat stable protein I (PHAS-I) pathway [68]. While CNIs remain the cornerstone of immunosuppression following solid organ transplantation [10], the use of mTOR inhibitors is growing because of the increasing prevalence of renal failure, cancer, and CAV in calcineurin inhibitors treated patients [69]. mTOR inhibitors form a complex with the intracellular binding protein FKBP-12 and arrest the cell cycle in the G1 phase, whereas, cyclosporine and tacrolimus, block T-cell activation induced by stimuli using Ca2+-dependent pathways [70-73]. mTOR inhibitors can affect the development and progression of CAV due to its non-immunologic effects, such as anti-fibrotic action and inhibition of angiogenesis [13, 74]. The commercially available mTOR inhibitors include sirolimus (SIR) and everolimus (EVE). SIR is a macrocyclic immunosuppressive agent that was originally investigated for
its anti-fungal properties [75]. The use of sirolimus (SIR) has been proposed as a substitute for CNIs in cardiac transplant patient based on its role in renal function preservation and prevention of chronic allograft vasculopathy [76-78]. In fact, SIR, can prevent vascular remodeling and neointimal proliferation, two key components of CAV, by inhibiting smooth muscle cell (SMC) and fibroblast proliferation [7, 28, 34, 94, 96, 105, 106]. SIR has been shown to reduce the incidence of acute rejection among renal-transplant recipients and to prevent CAV in animals [87]. Because of its potent anti-proliferative effects [88], SIR has also provided beneficial effects on regression of left-ventricular mass [89-91].

In addition to SIR, a novel mTOR inhibitor, everolimus (EVE), has been reported to attenuate and even prevent the development of CAV by inhibiting SMC proliferation and fibroblast proliferation, processes that are critical for the development of CAV [93, 94, 96-101]. In contrast to CNIs, EVE like SIR, does not inhibit the production of interleukins (ILs) resulting from antigen-induced activation of T cells [73, 102]. Rather, EVE inhibits growth-factor-mediated IL-2 and IL-15 pathways to inhibit T-cell and non-hematopoietic cell proliferation, thus inhibiting both the immune and non-immune response to the allograft [95, 103]. Consequently EVE inhibit SMC proliferation and neo-intimal thickening caused by non-immunological type injury [94, 104]. Indeed, EVE like SIR contribute to decrease the development of CAV [92].

Clinical studies demonstrated that EVE may prevent vascular remodeling, which is a key component of CAV [34, 94, 96] de novo following CTx [7, 28, 34, 94, 96, 105, 106]. mTOR inhibitors may provide some other beneficial ancillary anti-proliferative effects including improvement in coronary hemodynamics [28] and regression of cardiac hypertrophy, both leading to significant improvement in cardiac allograft function [100, 101,105]. However, mTOR inhibitors may have some deleterious effects on human vasculature. For instance, SIR treatment increased the risk of venous thromboembolism [28, 108] and long-term treatment with EVE has been associated with a significant increase in necrotic and calcified tissue in the human cardiac allograft [109]. Nevertheless, most of the biologic differences between SIR and EVE remain largely unknown.

Table I

<table>
<thead>
<tr>
<th>Systemic inflammation</th>
<th>Vascular inflammation</th>
<th>Neutrophil inflammatory responses</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inhibit cytokines release (IL-1β; IL-2; IL-6; IFN-γ; TNF-α)</td>
<td>• Endothelial dysfunction</td>
<td>• Decreased release of IL-8</td>
<td>28; 58;70;</td>
</tr>
<tr>
<td>• Increased ICAM-1 expression on human coronary artery endothelial cells</td>
<td>• Generation of free radicals</td>
<td>• Neutral effect on VEGF release</td>
<td>71; 72; 73;</td>
</tr>
<tr>
<td>• Increased ET-1 release; reduced NO synthesis</td>
<td>• Endothelial dysfunction</td>
<td>• Increased neutrophil adhesion on human umbilical vein endothelial cells (HUVECs)</td>
<td>74;</td>
</tr>
<tr>
<td>• Inhibit the synthesis of IL-2</td>
<td>• Generation of free radicals</td>
<td>• Decreased release of IL-8</td>
<td>28; 58; 71;</td>
</tr>
<tr>
<td>• Inhibit cytokines release (IL-1β; IL-2; IL-6; IFN-γ; TNF-α)</td>
<td>• Prevent vascular remodeling and neo-intimal proliferation</td>
<td>• Neutral effect on VEGF release</td>
<td>72; 73; 74;</td>
</tr>
<tr>
<td>• Suppression of IL-10</td>
<td>• Inhibit smooth muscle cells and fibroblast proliferation</td>
<td>• Decrease neutrophils adhesion to HUVECs</td>
<td></td>
</tr>
<tr>
<td>• Increased ET-1 release</td>
<td>• Anti-fibrotic activity</td>
<td>• Decrease neutrophils adhesion to HUVECs</td>
<td></td>
</tr>
<tr>
<td>• Reduced NO synthesis</td>
<td>• Prevent vascular remodeling and neo-intimal proliferation</td>
<td>• Decreased release of IL-8 and VEGF</td>
<td>7; 8; 28;</td>
</tr>
<tr>
<td>• Block cell cycle progression</td>
<td>• Inhibit smooth muscle cells and fibroblast proliferation</td>
<td>• Decrease IL-1RA release</td>
<td>35; 83; 84;</td>
</tr>
<tr>
<td>• Inhibit cytokines release</td>
<td>• Anti-fibrotic activity</td>
<td>• Decreased neutrophils adhesion to HUVECs</td>
<td>89; 90; 91;</td>
</tr>
<tr>
<td>• Block cell cycle progression</td>
<td>• Prevent vascular remodeling and neo-intimal proliferation</td>
<td>• Largest inhibition IL-8 release (-90%) in vitro</td>
<td>92; 93; 94;</td>
</tr>
<tr>
<td>• Inhibit cytokines release</td>
<td>• Inhibit smooth muscle cells and fibroblast proliferation</td>
<td>• Decrease release of VEGF</td>
<td>95; 103;</td>
</tr>
<tr>
<td>• Anti-inflammatory effect on TNF-related pathways</td>
<td>• Anti-fibrotic activity</td>
<td>• Increase release of IL-1RA</td>
<td></td>
</tr>
<tr>
<td>• Decrease neutrophils adhesion to HUVECs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


http://www.smartscitech.com/index.php/ics
We investigated the capacity of CsA, TAC, MPA, SIR and EVE alone or in combination to modulate the release of VEGF, IL-1RA and IL-8 by neutrophils under basal (PBS) and stimulated conditions. Under the basal (PBS) condition, pre-treatments of neutrophils with any IDs, individually or in combination, significantly decreased the release of VEGF, while the most significant decrease was observed using the mTOR inhibitors SIR or EVE. Moreover, under the various stimulated conditions, pre-treatment with SIR and EVE alone or in combination with CsA or TAC significantly decreased the release of VEGF by neutrophils, while no effects were observed with CsA only. Interestingly, when SIR was combined with MPA, we observed a complete or partial loss of the capacity of SIR to prevent VEGF release, whereas the capacity of EVE to prevent VEGF release was maintained when combined with MPA. (Figure 2)

Pre-treatments with any IDs, alone or in combination decreased IL-8 release by the neutrophil. The largest inhibitory effect on basal IL-8 release was observed with EVE (-90%) alone or in combination with any other ID. Interestingly, EVE was the only ID capable of promoting the release of the IL-1RA. The capacity of EVE to increase IL-1RA was maintained even when combined with CsA, 

(pro-inflammatory cytokine), and IL-1RA (anti-inflammatory cytokine). We observed that all agonists induced the release of VEGF, IL-1RA, and IL-8 by the neutrophils, with LPS having the most potent stimulating effect. (Figure 1)
TAC, or MPA. As such EVE appears to provide more potent anti-inflammatory effects than SIR.

In summary, we observed that among immunosuppressive agents both mTOR inhibitors, EVE and SIR, provide the most potent inhibitory effects on the neutrophils pro-inflammatory response. Globally, EVE was more powerful than SIR alone to decrease IL-8 and VEGF release from human neutrophils.

We further assessed the effects of different IDs used in monotherapy or in combination on neutrophil function adhesion in vitro by the assessment of adhesion on human umbilical vein endothelial cells (HUVEC) or human extracellular matrix (hECM). We observed that when stimulated with TNF-α, pre-treatment with CsA or MPA provided a non-significant increase of neutrophils adhesion to endothelial cells, whereas pre-treatment with TAC, SIR or EVE decreased neutrophil adhesion by about 74%. This effect appears mediated by the activation of the β2-integrin complex (CD11b/CD18). These observations proposed some novel mechanisms on the interplay between neutrophil-mediated pro-inflammatory responses and IDs. The clinical significance of these findings needs to be further investigated.

**Conclusions**

IDs agents provide their immunosuppressive effects via distinct cellular targets and as such exhibit some other
specific biologic effects on the myocardial and on the vascular structures and functions. These agents also yield some different pro and anti-inflammatory effects on the neutrophil but also at the level of cardiac and vascular tissues. Because the neutrophils play a significant role on the development and on the progression of CAV, the biologic effects of IDs on these specific cells are likely clinically significant. Our recent in vitro data showed that EVE is likely the most potent IDs to prevent cytokine release and neutrophil adhesion, two key mechanisms involved in the development and progression of CAV. These findings may lead to the understanding and to the future development of innovative prophylactic and therapeutic strategies using EVE alone or in combination following organ transplantation.

Conflicting interests

The authors have declared that no conflict of interests exist.

Abbreviations

CAV: coronary allograft vasculopathy; CNIs: calcineurin inhibitors; CsA: cyclosporine A; CTx: cardiac transplantation; ET-1: endothelin-1; EVE: everolimus; FKBP12: FK506-binding protein 12; HeCM: human extracellular matrix; HUVEC: human umbilical vein endothelial; ICAM-1: intercellular cell adhesion molecule-1; ID: immunosuppressive drugs; ILs: interleukins; MHC: major histocompatibility complex; MMF: mycophelolate mofetil; NOS: nitric oxide synthase; PDGF: platelet derived growth factors; PHAS-I: phosphorylatable heat stable; ROS: reactive oxygen species; SIR: sirolimus; SMC: smooth muscle cells; TAC: tacrolimus; TGF-α: transforming growth factor-alpha; VCAM-1: vascular cell adhesion molecule-1; VEGF: vascular endothelial growth factor.

Author contributions

D.C. performed laboratory assays and wrote the manuscript, M.G.S. developed the assays on neutrophils, reviewed the manuscript and provided significant input on the intellectual content and M.W. planned the manuscript, supervised Ms Chaar for manuscript preparation and provided significant input on the intellectual content.

References


17. Valantine HA. Cardiac allograft vasculopathy: central role of
endothelial injury leading to transplant "atheroma". Transplantation 2003; 76:891-899.


travocilimus-based immunophrophylaxis improves cholesterol profile in heart transplant recipients with treated but persistent dyslipidemia: the Canadian multicentre randomized trial of tacrolimus vs cyclosporine microemulsion. J Heart Lung Transplant 2005; 24:798-809.


82. Radovancevic B and Vrtovec B. Sirolimus therapy in cardiac transplantation. Transplant Proc 2003; 35:171S-176S.


