Clinical recommendations for the use of everolimus in heart transplantation

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Abstract

Proliferation signal inhibitors (PSIs), everolimus (EVL), and sirolimus are a group of immunosuppressor agents indicated for the prevention of acute rejection in adult heart transplant recipients. Proliferation signal inhibitors have a mechanism of action with both immunosuppressive and antiproliferative effects, representing an especially interesting treatment option for the prevention and management of some specific conditions in heart transplant population, such as graft vasculopathy or malignancies. Proliferation signal inhibitors have been observed to work synergistically with calcineurin inhibitors (CNIs). Data from clinical trials and from the growing clinical experience show that when administered concomitantly with CNIs, PSIs allow significant dose reductions of the latter without loss of efficacy, a fact that has been associated with stabilization or significant improvement in renal function in patients with CNI-induced nephrotoxicity. The purpose of this article was to review the current knowledge of the role of PSIs in heart transplantation to provide recommendations for the proper use of EVL in cardiac transplant recipients, including indications, treatment regimens, monitoring, and management of the adverse events.

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1. Introduction

Proliferation signal inhibitors (PSIs) (also known as mTOR inhibitors) constitute a family of powerful immunosuppressors that inhibit the intracellular signals regulating cell growth and division [1]. This mechanism of action is based on mTOR (mammalian target of rapamycin) blockade and the consequent inhibition of kinase p70 S6, resulting in B and T cell and nonhematopoietic cell cycle arrest in phase G1 [2]. Two PSIs are available for clinical use in solid organ transplantation: sirolimus (SRL; Rapamune; Wyeth Pharmaceuticals, Maidenhead, United Kingdom [3]) and, more recently, everolimus (EVL; Certican; Novartis Pharma AG, Basel, Switzerland [4]). Both drugs have a similar chemical structure but different pharmacokinetic profiles, a fact that may be clinically relevant in relation to tolerability. The half-life of EVL is shorter than that of SRL (28 hours vs 62 hours) [5] and reaches stable therapeutic blood concentrations more quickly. Several long-term clinical trials in kidney and heart transplantation patients have demonstrated the immunosuppressive efficacy of EVL-based treatment [6-8], together with certain additional benefits such as the prevention of graft vascular disease and posttransplantation malignancies.

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1 Dr Nicolás Manito and Dr Juan F Delgado have contributed equally to the development of this article.

0955-470X/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.trre.2010.01.005
Despite a growing literature of EVL in heart transplantation, there is need for recommendations for the appropriate use and management of EVL in clinical practice. In this article, a group of experts in heart transplantation review the current knowledge of the role of PSIs in heart transplant recipients using data from their clinical experience (which includes approximately 600 EVL-treated patients for the past 8 years) and published studies. Based on such data, clinical recommendations for the use of EVL in heart transplantation are suggested.

2. Indications of EVL in heart transplantation

2.1. De novo heart transplant recipients

Everolimus, in combination with cyclosporine (CsA) and corticosteroids, is indicated for the prevention of acute rejection in adult heart transplant recipients [4,10]. Clinical data are lacking concerning the concomitant administration of EVL and tacrolimus in de novo heart transplant recipients. However, the combination of tacrolimus and SRL (plus steroids) has been evaluated in this population in a randomized clinical trial and compared with 2 other groups: tacrolimus + mycophenolate mofetil (MMF) + steroids and CsA + MMF + steroids [11]. Regarding the primary end point (incidence of International Society of Heart and Lung Transplantation grade 3A or greater rejection or rejection with hemodynamic compromise that requires therapy within the first 6 months), there were no significant differences at 6 months and 1 year between the 3 groups. In this context, and in the absence of possible contraindications (Table 1), EVL can be recommended in most de novo heart transplant recipients, though there are certain patient groups in which the antiproliferative effects of the drug may prove particularly beneficial (Table 2), such as patients at high risk of developing cardiac allograft vasculopathy (CAV), nephrotoxicity induced by calcineurin inhibitors (CNIs), or malignancies.

Several prevention strategies have been used in the early phases of heart transplantation to minimize CAV. The better control of cardiovascular risk factors and the routine administration of statins to all patients after transplantation have clearly reduced morbidity and mortality and the progression of CAV. Other drugs, such as calcium antagonists, angiotensin-converting enzyme inhibitors, and anticytomegalovirus treatments have also shown promising results in this field [12]. Regarding PSIs, one of their main advantages is the prevention of CAV, and in fact, it represents their most common application in clinical practice. The original study of EVL in heart transplantation compared of the efficacy of 2 daily doses of the drug (1.5 or 3 mg), together with CsA and corticosteroids in 634 de novo patients vs azathioprine (AZA) [10]. After 12 months, coronary intravascular ultrasound (IVUS) revealed less progression of CAV in the 2 groups treated with EVL as evidenced by less increase in maximum intimal thickness (MIT) and a lower incidence of CAV defined as MIT increase of 0.5 mm or more. The severe acute rejection rate as confirmed by biopsy (≥3A) and the cytomegalovirus infection rate were also lower with EVL. These early results were further corroborated with longer follow-up at 2 and 4 years [8,13], indicating that EVL treatment was associated with a lower incidence of CAV-related major cardiovascular events (8% vs 13%; \( P = .03 \)) and with a lesser mean cost of treatment for such complications [8]. Studies of SRL have reported similar results for prevention of CAV [14,15]. Furthermore, a growing body of evidence that PSIs reduce the incidence factors have previously been linked to pathophysiology of CAV. For example, in a recent study of 176 de novo patients, an EVL regimen consisting of carefully controlled concentrations (trough blood levels, 3–8 ng/mL) with lowered doses of CsA was compared to a regimen of standard doses of CSA and MMF [16]. After 1 year, the incidence of cytomegalovirus infection (positive antigenemia or polymerase chain reaction detection, 4% vs 17%; \( P = .01 \)) and of acute rejection rate as confirmed by biopsy of 3A or greater (23% vs 30%) was significantly lower with EVL [17]. Indeed, despite MMF is the most common de novo immunosuppressive treatment in heart transplant recipients [18–20], its impact on preventing CAV has been less well documented than that of PSIs, and IVUS studies have only revealed a nonsignificant favorable trend compared to AZA [20].

Malignancies are another major limiting factor in the long-term outcomes of heart transplant patients [21,22]. Some studies suggest that the type of immunosuppression used is an important cancer risk factor, and oncogenic mechanisms have been described for CNIs [23–26] and AZA [27,28], whereas the role of MMF has not been fully established to date [25,29–32]. In contrast, solid evidence has been gained relating PSIs to a clear reduction in post-transplant cancer risk, particularly compared to CNI-based treatment regimens [9,33–35], so the introduction of EVL or SRL constitutes the most frequent strategy regarding immunosuppression for the prevention of malignancies in heart transplant recipients. In 2 large renal transplant studies, both early and late conversion from CNI to SRL were associated with significant reductions in both cutaneous and noncutaneous tumors and a delay in the mean time of appearance of such tumors [34,35]. In addition, an analysis of more than 33 000 patients of the American Kidney Registry revealed that the combination of EVL or SRL with a CNI lowered the risk of cancer compared to CNI monotherapy (0.6% vs 1.8%; \( P < .05 \)) [9], corroborating the findings observed in de novo studies with both drugs.
(incidence approximately 2% after 2 years with PSI + CNI vs 7% with CNI in the absence of PSI) [33,36]. Consequently, an EVL-based regimen in de novo patients with cancer risk factors could be beneficial.

In general, the use of EVL in a de novo regimen requires the concomitant administration of CNI to ensure adequate antirejection efficacy during the first year after transplantation [37,38]. However, there is also evidence suggesting that EVL would allow for delayed introduction of CsA, thereby, providing an alternative approach for reducing CNI nephrotoxicity in the early posttransplant period in patients with poor preoperative kidney function [39]. González-Vilchez et al [40] evaluated an immunosuppressive regimen consisting of either EVL or SRL without CNI, in 20 de novo patients with pretransplant kidney failure defined by a glomerular filtrate rate (GFR) less than 30 mL/min per 1.73 m². After 1 month, there was a significant improvement in kidney function (>65 mL/min per 1.73 m²), which remained stable thereafter. However, 11 patients had acute rejection, 5 of whom had received EVL with no induction therapy. Furthermore, in 50% of the cases, a CNI had to be introduced in place of the PSI, due to adverse effects. Thus, it is generally

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DM indicates diabetes mellitus; PTLD, posttransplantation lymphoproliferative disease.
* First 6 posttransplantation months.
† More than 6 months posttransplantation.
advised that CNI-free regimens should be reserved only for well-selected cases and should be used in combination with induction therapy to avoid the risk of acute rejection.

2.2. Conversion to EVL

2.2.1. Early conversion (≤6 months after transplantation)

Taking into account that most of the factors involved in the pathophysiology of the most important post heart transplantation problems (such as CAV, nephropathy, and malignancies) can be present in the first months posttransplantation, any prevention strategy should be started as early as possible. From an empirical point of view, we consider the first 6 months after heart transplantation a critical period in which the maximal load of immunosuppression is usually given and higher rates of adverse events can be found. In this context, a lack of immunosuppressive efficacy, intolerance to other drugs, or the prevention of CNI nephrotoxicity (see Section 2.2.2) are some of the common reasons for introducing EVL during the first months after heart transplantation (Table 2). In general, this strategy offers additional advantages, particularly in the prevention of CAV progression, and is increasingly common in clinical practice. In a recent study, 29 heart transplant patients (average time of transplantation, 3.8 + 3.4 years) were converted to an SRL-based regimen without CNI (+MMF/AZA) and were compared with a series of 40 patients treated with MMF/AZA and CNI [41]. One year after conversion, the mean plaque volume and plaque index observed with IVUS were seen to remain stable in the PSI group (+0.1 mm³/mm, \( P = .63; +0.1\% , P = .94\)) in contrast to the significant increase recorded in the control group (+1.19 mm³/mm, \( P = .0003; +6\% , P = .0001\)). However, when separately considering the patients converted more than 2 years after heart transplantation, the observed differences were limited only to progression of the plaque index (no differences were observed regarding the plaque volume between the PSI group and the CNI group), whereas in patients enrolled within 2 years after transplantation, both the increases in plaque volume and plaque index were significantly smaller in the SRL group compared with the CNI group. These findings suggest that the sooner the PSI is introduced, the greater the benefits in CAV prevention are achieved, and supports an early conversion strategy.

2.2.2. Intermediate and long-term heart transplant recipients (>6 months after transplantation)

Renal failure is a frequent complication in heart transplant recipients and is consistently correlated to poorer outcomes [42]. The CNI nephrotoxicity is the main causal factor that can potentially be ameliorated using low-dose or CNI-free regimens. Proliferation signal inhibitors are not nephotoxic per se, though their combination with full doses of CsA or tacrolimus can worsen the nephotoxic effects of CNIs unless careful attention is paid to drug doses and blood levels [10,14]. Many studies in maintenance heart transplant recipients have shown that the introduction of EVL or SRL, accompanied by gradual CNI reduction [43-47] or withdrawal [45,48-58], is generally associated with stabilization or significant improvement in kidney function, without loss of immunosuppressive efficacy. In some series, this has implied a mean reduction in plasma creatinine levels of approximately 25% to 60%. In one study, 39 maintenance heart transplant recipients with renal failure were randomized to either CNI conversion to SRL or to low-dose CNI therapy [59]. After 6 months, and although the CNI group showed stable kidney function, it was in the PSI group where clear improvement was noted, with a mean increase in glomerular filtration rate from 49 to 62 mL/min per 1.73 m². This indicates that better results are probably obtained with CNI withdrawal. Recently, the first results have been reported involving an EVL-based regimen without CNI in 60 maintenance heart transplant recipients [60]. In these patients, the conversion to EVL maintained immunosuppressive efficacy and improved renal function after 6 months (serum creatinine level, 2.1 vs 1.5 mg/dL; \( P = .001\); GFR, 42.2 vs 62 mL/min per 1.73 m²; \( P = .018\)), as well as the CNI-related adverse effects (tremor, hirsutism, gingival hyperplasia, and peripheral edema). Similar results have also been observed at 12 months in 56 patients by Moro et al [48]. In general, the introduction of EVL with CNI dose adjustment or withdrawal for the preservation of kidney function should be evaluated on an individualized basis in intermediate and long-term patients, including careful consideration of acute rejection history and presence/absence of CAV. The EVL regimens with low dose (or no) CNI should be introduced early because the results for conversion to PSIs for patients in advanced stages of kidney damage indicate that the chances for improvement are poor [61-63]. Indeed, some studies suggest that kidney function need not be severely impaired to institute conversion to EVL with CNI reduction. To realize clear benefit, a GFR of more than 40 mL/min per 1.73 m² is advised, though even in patients with poorer creatinine clearance, conversion to EVL with CNI reduction may also be effective in slowing the deterioration of kidney function [37].

For established CAV, 2 single-center studies suggest clinical benefits for halting or slowing progression after the introduction of a PSI [64,65]. Conversion from MMF/AZA to SRL is associated with a reduction in the progression of MIT and with fewer CAV-related adverse events, such as mortality, myocardial infarction, or the need for retransplantation. Although these results require confirmation in multicenter, randomized controlled trials, the introduction of EVL or SRL after angiographic or IVUS detection of CAV is becoming an increasingly common practice in the clinical management of heart transplant patients [12,66].

The initiation of a PSI in heart transplant patients who have developed malignancies is likewise a growing practice. Although the existing evidence is limited and comes from small kidney transplant series, EVL is the subject of an advanced clinical development program in oncology, yielding important results in the prevention of disease
progression and survival [67]. In general, CNI conversion to PSI is associated with a 50% to 70% remission rate in posttransplant skin cancer lesions [68,69]. In transplanted patients with Kaposi’s sarcoma, the introduction of a PSI to replace CNI/MMF has demonstrated partial or complete disease regression after 2 to 8 months in 70% to 100% of the cases [70-74]. Some studies also suggest that PSIs, together with other standard therapeutic measures, are potentially effective against posttransplant lymphomas [68,75,76]. In a series of 19 kidney transplant patients with lymphoma, the CNI was discontinued and replaced with EVL/SRL. In addition, 6 patients received rituximab, and 6 received citoxon, hydroxydoxorubicin oncovin, prednisone (CHOP) chemotherapy [77]. Fifteen of the patients showed complete disease remission that persisted for the full duration of the follow-up (6–156 months). In relation to solid organ tumors, there have been reports of patients with lung or ovarian metastasis after liver transplantation due to hepatocarcinoma in which the introduction of SRL led to rapid disappearance of the lesions [78,79]. In general, clinical experience is increasing in this field, and a recent study involving 10 liver transplant patients (6 of them with solid tumors such as hepatocarcinoma, esophagus, lung, and larynx) has suggested that the conversion to EVL may increase the probability of survival, on comparing the results obtained with those of a similar historical cohort not treated with the PSI [80]. On the basis of the limited available data cited above, we conclude that in certain heart transplant recipients who develop malignancies (Table 2), it seems logical to consider introducing a PSI as part of their immunosuppressive regimen. Such an intervention should be evaluated on an individualized basis and as part of a multidisciplinary management strategy.

3. Recommended EVL treatment regimens and doses

3.1. De novo regimens

In de novo patients, EVL should be started as soon as possible after transplantation, together with CsA and corticosteroids, at a dose of 0.75 mg every 12 hours; patients with mild to moderate liver dysfunction require much lower doses, often less than half the standard dose [4]. The monitoring of plasma drug concentrations is required (see Section 4) to ensure that therapeutic levels of 3 to 8 ng/mL are attained. Such systemic exposure offers adequate antirejection efficacy without increasing the appearance of adverse effects [81].

An important consideration in the de novo treatment with EVL is the possibility of lowering the CsA dose to prevent the nephrotoxic effects of the latter drug while maintaining immunosuppressive efficacy [16,82]. In an observational study in 52 de novo heart transplant patients, an EVL-based regimen with lowered CsA doses demonstrated the same efficacy but with greater protection of kidney function than standard treatment with CsA/MMF. After 12 months, efficacy was high in both groups (acute rejection rates, 23% EVL vs 28% MMF), although a lowering of creatinine levels from 1.67 to 1.53 mg/dL was observed with the PSI, whereas in the MMF group, the levels increased from 1.22 to 1.99 mg/dL [82]. These and other published data suggest that in de novo patients consideration should be given to early reduction of CsA after introducing EVL with the goal of preserving kidney function, according to the regimen shown in Fig. 1 (A). Furthermore, a treatment protocol based on EVL, MMF/AZA, and corticoids can help delay the introduction of CNI in some de novo patients with poor pretransplantation kidney function [39,40]. In these cases, it is advisable to adjust the EVL dose to achieve high plasma levels (6–8 ng/mL), with the concomitant use of an induction agent such as an anti–interleukin-2 receptor antagonist or an antithymocyte globulin.

3.2. Conversion regimens

Based on published data and clinical experience, Fig. 1 (B) shows the EVL conversion protocols recommended for the different patient profiles in which a PSI is indicated. In general, the experience gained in intermediate- and long-term heart transplant patients suggests that the conversion to EVL with a concomitant reduction in the levels of CsA stabilizes kidney function without increasing the risk of rejection [43,46]. The practical application of this strategy is to simultaneously discontinue MMF/AZA and start EVL at a dose range of 0.5 to 0.75 mg/12 h, targeting a therapeutic blood level of 3 to 8 ng/mL [83]. Once this therapeutic blood level is achieved, the CsA dose is gradually reduced, in increments of 25% reduction, to achieve target CsA \( \text{C}_0 \) levels of 50 to 100 ng/mL [83]. In patients with more profound CNI nephrotoxicity, an alternative strategy is to establish a CNI-free regimen using EVL [48-50]. In these cases, it has been suggested that EVL should be initiated at a dosage of 0.75 mg/12 h, followed by a 25% to 30% reduction in CNI after 3 days, with completed discontinuation between the second and third week if stable therapeutic EVL levels (3–8 ng/mL) have been achieved [37,49]. During this process of CNI discontinuation, concomitant MMF and corticoids at full doses are required [37], together with rigorous surveillance for acute rejection by endomyocardial biopsies performed within 30 to 90 days after discontinuation of CNI.

To date, all published beneficial effects of PSIs in patients diagnosed with CAV have been obtained in combination with a CNI [64,65,84]. Consequently, after detection of CAV, EVL should be introduced for MMF/AZA, with concomitant lowering of the CNI dose and monitoring of the blood levels of drugs. In patients with severe nephrotoxicity, discontinuation of the CNI may be considered using the same approach described above, with the initiation of EVL and MMF [85].

Finally, in relation to patients with post heart transplantation malignancies, the benefits of the conversion from CNI to EVL are likely the result both of the antitumor effects of
PSIs and the withdrawal of potentially oncogenic drugs such as CsA or tacrolimus [68,70-73,77,80,86]. Regarding antimitotic drugs, it is remarkable that clear carcinogenic effects have been described with AZA [27,28], whereas the in vitro results obtained with MMF are less conclusive [25]. In the clinical setting, some registry data suggest that MMF could be associated with a reduced posttransplantation cancer risk, as well as an increase in the mean time of appearance of the first malignancy [30]. As a consequence, the withdrawal of AZA and the introduction of MMF at low doses is a common recommended strategy for these patients in clinical practice. Patients with malignancies and CAV who develop acute rejection after the discontinuation of the CNI and the introduction of EVL present yet another
level of complexity in their management. In these patients, the antiproliferative effects of EVL could be beneficial for the prevention of the progression of both pathologic conditions, so the continuation of the PSI should always be considered. Taking this into account, in these cases, it is recommended to stop MMF and reintroduce the CNI at low doses to prevent rejection.

4. Monitoring EVL levels

To detect subtherapeutic concentrations or levels in excess of the recommended limits, which may give rise to adverse effects, EVL trough blood levels must be monitored as proposed in Fig. 2, after its initiation. The goal is to achieve the established therapeutic range of 3 to 8 ng/mL [81] based on the required dose adjustments in response to drug concentration measurements obtained more than 4 to 5 days after the preceding change in dose. In general, it has been estimated that 2 of every 3 patients treated with 1.5 mg/d of EVL achieve the target therapeutic plasma levels within 6 days [81]. Once the drug concentrations have stabilized within the recommended range, the subsequent measurements can be spaced according to routine practice, though any change in EVL dose or in the concomitant immunosuppressive drugs must be accompanied by measurement of both EVL and CNI blood levels because of the significant alterations levels that have been observed after dose adjustments of either drug [87]. This cautious approach incorporating regular drug level monitoring is also recommended when EVL is used in combination with other drugs that used the isoenzyme CYP3A4 of the hepatic P450 cytochrome system, the main enzyme responsible for the metabolism of EVL [2]. Drugs that induce or inhibit this isoenzyme (Fig. 3) require additional monitoring, as do patients with treatment failure, poor liver function, or suspected serious adverse effects.

The development of an immunoassay kit for the determination of EVL trough blood levels has made it possible for any clinical laboratory to obtain reliable results within 2 hours (precision variation coefficient of 6% and 11% for EVL trough blood levels of 2.5 and 25 ng/mL, respectively), with an adequate detection range (2–40 ng/mL) [88]. The drug levels can also be determined by liquid chromatography with mass spectrometry [89] (limit of quantification, 0.3 ng/mL).

5. Management of the adverse effects of EVL

The frequent appearance of adverse effects requiring specific treatment and/or drug reduction/withdrawal is the main inconvenience of PSIs [10,14]. In the original study of EVL, 30% of the patients treated with 1.5 mg/d had to interrupt therapy because of intolerance [10]; however, it has subsequently been demonstrated that plasma levels maintained between 3 and 8 ng/mL considerably reduced the risk of adverse effects. In a more recent study of de novo, a 15% dropout rate was observed with such treatment strategy [90,91]. Table 3 shows the main adverse effects associated with EVL, along with the recommendations for their management based on published articles and on the clinical
experience of the authors. Some of the most relevant aspects are discussed below.

The use of PSI in heart transplant recipients is usually associated with a significant increase in blood cholesterol and triglycerides [10,14]. The causes underlying such hyperlipidemia are not fully clear, though murine models have shown that EVL alters lipid homeostasis in peritoneal macrophages, with an increase in cholesterol esterification [92]. In general, the hypercholesterolemia can be controlled with statins [37,38,93] and a number of publications have demonstrated the benefits (in long-term survival and CAV prevention) of introducing such treatment in heart transplant recipients [94-97]. In addition, the combination of EVL and fluvastatin increased the antiproliferative activity of the PSI

Fig. 3. Pharmacologic interactions with EVL [37,83,88,120-123]. * indicates that given the magnitude of the interaction between ketoconazole and EVL (EVL C_{max} × 3.9; EVL AUC × 15; EVL t_{1/2} × 1.9) [121], it is recommended to avoid concomitant administration of the 2 drugs as far as possible. **, If a CsA-free regimen is planned from EVL-based treatment, it must be taken into account that on withdrawing CsA the EVL levels decrease. No pharmacologic interactions with tacrolimus are known.
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<td></td>
<td></td>
<td>Use of lipid-lowering agents [37,38,93]</td>
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<td></td>
<td></td>
<td>Associate ezetimibe and/or fatty acids in hyperlipidemia that is severe or poorly controlled with the above [101,102]</td>
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<td>Delayed wound healing</td>
<td>Observed in 7%–52% of de novo patients with PSI [11,14,107,108] Probably less important with EVL than with SRL</td>
<td>Evaluate nonintroduction of PSI in de novo patients with BMI &gt; 32 kg/m² [128]</td>
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<td>Use of closed suction drains [128]</td>
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<td>Use of meticulous surgical techniques [37,38]</td>
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<td>Use of nonabsorbable sutures and delay their extraction (2–3 wk) [38]</td>
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<td>Delay introduction of EVL 3–7 d in de novo patients [37]</td>
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<td>Withdraw EVL 1 wk before in patients needing major surgery and reintroduce after 10–15 d [37]</td>
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<td></td>
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<td>Minimize corticoid use [38]</td>
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<tr>
<td>Bacterial infections</td>
<td>Observed in approximately 30% of de novo patients with PSI [10,14]</td>
<td>Specific treatment</td>
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<tr>
<td>Angioedema</td>
<td>Described in 6 heart transplant recipients converted to EVL [109]</td>
<td>Consider withdrawing EVL in repeat episodes</td>
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<td>Withdraw ACEIs [37]</td>
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<td></td>
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<td>Reduce EVL (3–4 ng/mL) or withdraw [37,38]</td>
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<td>Peripheral edema</td>
<td>Observed with PSI in up to 31%–76% of de novo heart transplant recipients [14,129]</td>
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<td>Evaluate reduction or withdrawal of EVL if platelet count &lt; 50 000 [83]</td>
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<td>Lymphopenia</td>
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<td>Evaluate reduction or withdrawal of EVL</td>
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<td>Interstitial pneumonitis</td>
<td>Some cases have been reported in PSI-treated heart transplant recipients [110-115]</td>
<td>Consider reduction or temporary/permanent withdrawal of VL [37,111,112,114]</td>
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<td></td>
<td></td>
<td>Administration of corticoids [37,111,112]</td>
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<tr>
<td>Cutaneous disorders</td>
<td>Observed in 31% of de novo patients with EVL [129]</td>
<td>Usually improves spontaneously within a few weeks</td>
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<td>Acne</td>
<td></td>
<td>Topical dermatologic treatment [37,38]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Evaluate EVL dose reduction or change to other PSI [38]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discard infectious origin</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>Evaluate EVL dose reduction</td>
</tr>
<tr>
<td>Oral aphthae</td>
<td>Observed in up to 20% of de novo patients with SRL [14]</td>
<td>Dermatologic treatment</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Observed in 18%–32% of de novo patients with PSI [14,129]</td>
<td>Discard viral/fungal infection</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Observed in some heart transplant recipients converted to SRL [119]</td>
<td>Perform renal biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider reduction/withdrawal of EVL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use ACEIs/ARB-II [119]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid conversion to PSI in patients with proteinuria &gt; 800 mg/d [117]</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
in 2 experimental studies, suggesting the possible existence of synergy between the 2 treatments [98,99]. Fibrates in turn are useful for the treatment of patients with hypertriglyceridemia [93], though caution is advised for their use with statins, due to the increased risk of rhabdomyolysis. Although pravastatin has shown to have a lower incidence of myopathy compared with simvastatin [94], the concomitant use of any statin with a PSI should be accompanied by regular monitoring creatine phosphokinase levels [100]. Recent studies of ezetimibe in heart transplant recipients who had a poor response or intolerance to statins have reported significant reductions in total cholesterol, low-density lipoprotein cholesterol, and triglycerides [101,102]. Consequently, ezetimibe should be considered in cases of statin intolerance and/or severe hyperlipidemia.

Although not homogeneously reported in clinical trials [14], peripheral edema (especially malleolar edema or lymphedema) is a frequent, and sometimes important, adverse event observed with EVL and SRL in clinical practice. Proliferation signal inhibitors affect endothelial permeability by increasing cellular oxidative stress and through the release of prostacyclin (which is related to vasodilation). Proliferation signal inhibitors have also been associated with decreased expression of the vascular endothelial cadherin and with lymphangiogenesis inhibition [103-106]. In general, with just a reduction in the dose of the PSI mild cases can improve within some weeks (drug withdrawal should only be considered in severe or persisting cases). Other options in the management of edemas are the use of diuretics or the introduction of changes to the antihypertensive treatment.

Increase in surgical wound complications after transplantation have been linked to the use of SRL compared with AZA and MMF, suggesting a class effect of PSI [11,14,107]. However, in the original study of EVL there was only an increased risk of lymphocele and severe pericardial effusion. In comparison to MMF, de novo treatment with EVL had a similar incidence of adverse effects at the incision site (dehiscences, secretions, lymphocele, and infections, 8% vs 7%), pleural effusions (25% vs 22%), and cardiac tamponade (approximately 5% in both cases), though the pericardial effusion rate was greater with the PSI (25% vs 35%) [108]. The delayed introduction of EVL in the de novo protocols (≥72 hours posttransplantation [10]) may facilitate adequate wound healing to a greater extent compared with the early introduction of SRL [14]. This delay, together with optimal surgical techniques, is required for preventing postoperative wound healing complications [107].

An infrequent yet potentially serious adverse effect of EVL is angioedema. In a series of 114 heart transplant patients, the conversion to EVL was followed within a few weeks by the appearance of lingual angioedema in 6 patients [109]. In 5 cases, intravenous treatment with 250 mg of prednisolone and 2 mg of the antihistamine drug clemastine fully resolved the symptoms, whereas one patient with recurrent episodes required the interruption of EVL. Other allergic reactions associated with the use of PSI are skin problems such as acne or rash, and interstitial pneumonitis, without evidence of infection [110-115]. In general, such pneumonitis is of allergic origin and not dose related. The administration of corticosteroids and/or PSI withdrawal usually leads to resolution of the clinical and radiologic symptoms [111,112,114].

Finally, the appearance or worsening of proteinuria has been documented in kidney transplant patients converted to PSIs, particularly in those with high preconversion proteinuria levels. As a result, it has been established that such drugs should not be administered to patients with proteinuria more than 800 mg/d [116,117]. The mechanism by which PSIs induce proteinuria is not clear, though it could be related to diminished tubular protein reabsorption secondary to a decrease in the activity of vascular endothelial growth factor [118]. In heart transplant patients, there are few data because proteinuria is not usually determined in routine clinical practice. In 49 long-term patients, the conversion from CsA to a SRL-based regimen significantly increased proteinuria from 0.13 to 0.23 g/d at 24 months postswitch (P = .0024) and the number of patients with severe proteinuria (>1 g/d) increased from 11% to 23% [119] (P = .006). These patients showed decreased renal function at the end of follow-up (39.6 vs 29.2 mL/min per 1.73 m²; P = .125). The effects of EVL in this context are still unknown, although it is advisable to monitor proteinuria after introducing EVL. In general, studies are needed to establish the role of PSIs in increasing the risk of proteinuria in heart transplant recipients.

Acknowledgments

The authors thank Dr Hannah Valantine of the Falk Cardiovascular Research Center (Stanford University Medical School, CA) for revision of the article.

Editing support from Ogilvy Healthworld Barcelona is also acknowledged.

The present article has been developed from the contents of 2 meetings of experts in heart transplantation, in which practical issues were addressed in relation to the usefulness and management of everolimus in heart transplant recipients. Both meetings were sponsored by a grant of Novartis Pharmaceuticals, Inc.

The authors report no conflict of interest.

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