Review Article

 Everolimus in Heart Transplantation: An Update

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The evidence base relating to the use of everolimus in heart transplantation has expanded considerably in recent years, providing clinically relevant information regarding its use in clinical practice. Unless there are special considerations to take into account, all de novo heart transplant patients can be regarded as potential candidates for immunosuppression with everolimus and reduced-exposure calcineurin inhibitor therapy. Caution about the use of everolimus immediately after transplantation should be exercised in certain patients with the risk of severe proteinuria, with poor wound healing, or with uncontrolled severe hyperlipidemia. Initiation of everolimus in the early phase aftertransplant is not advisable in patients with severe pretransplant end-organ dysfunction or in patients on a left ventricular assist device beforetransplant who are at high risk of infection or of wound healing complications. The most frequent reason for introducing everolimus in maintenance heart transplant patients is to support minimization or withdrawal of calcineurin inhibitor therapy, for example, due to impaired renal function or malignancy. Due to its potential to inhibit the progression of cardiac allograft vasculopathy and to reduce cytomegalovirus infection, everolimus should be initiated as soon as possible after heart transplantation. Immediate and adequate reduction of CNI exposure is mandatory from the start of everolimus therapy.

1. Introduction

The mammalian target-of-rapamycin inhibitor (mTOR) everolimus has been licensed in Europe since 2004 for the prevention of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic kidney, liver or heart transplant. Everolimus is currently the only mTOR inhibitor approved for use in heart transplantation. It was developed to improve the pharmacokinetics of the mTOR inhibitor sirolimus through a stable 2-hydroxyethyl chain substitution at position 40 of the sirolimus molecule [1]. This change confers a shorter half-life, permitting faster reduction or elimination of everolimus exposure and obviating the need for a loading dose.

In a pivotal double-blind phase 3 (B253) trial in de novo heart transplant recipients published in 2003,
Eisen et al. demonstrated that everolimus provided equivalent immunosuppressive efficacy to azathioprine [2]. Inhibition of vascular smooth muscle cell proliferation by everolimus reduced intimal thickening and lowered the incidence of cardiac allograft vasculopathy (CAV). Based on these findings and early clinical experience in Germany and Austria, recommendations on the use of everolimus in heart transplantation were developed at two expert meetings held in 2004 [3] and 2006 [4]. Since then, the evidence base relating to everolimus in heart transplantation has expanded substantially with additional randomized studies in de novo [5] and maintenance [6–8] heart transplant patients. Recently, results from the 24-month, international, randomized, open-label study A2310 [9] have been published, refocusing attention on the use of everolimus in de novo heart transplant patients. This paper considers the current data set and considers the implications for use of everolimus in this setting.

2. Everolimus in Heart Transplant Recipients: The Key Studies

2.1. Study Designs. The key studies evaluating the de novo use of everolimus following heart transplantation and their primary endpoints, are summarized in Table 1. In a 24-month, multicenter, randomized, double-blind, double-dummy, phase 3 study (B253), the efficacy, safety, and tolerability of two fixed doses of everolimus (1.5 and 3.0 mg/day) were compared to azathioprine in 634 de novo heart transplant recipients [2]. All patients received a triple drug regimen that included standard-dose cyclosporine (CsA) and corticosteroids. In the multicenter, randomized A2411 trial (n = 176), the immunosuppressive regimen was changed to concentration-controlled everolimus (initial dose 1.5 mg/day, target trough level C0 3–8 ng/mL) and reduced-exposure CsA to examine whether renal toxicity was reduced compared to mycophenolate mofetil (MMF, 3 g/day) with standard CsA [5]. Both groups received steroids and antibody induction therapy according to local practice. In an observational study by Lehmkuhl et al., everolimus (C0 3–8 ng/mL) with low-exposure CsA was compared to MMF (mean dose 1.25–2.5 g/day) in combination with standard CsA in 52 de novo heart transplant patients [10]. All patients received induction with antithymocyte globulin (two doses of 2.5 mg/kg) and steroids. Mean CsA C0 decreased by 58% from week 2 to month 12 in the everolimus group versus 35% in the MMF cohort (mean [SD] at month 12: 101 [26] ng/mL) versus 160 [41] ng/mL.

The A2310 trial was an international, open-label, 24-month study in which 721 de novo heart transplant recipients were randomized to (i) standard everolimus trough concentration (3–8 ng/mL), to (ii) high everolimus trough concentration (6–12 ng/mL) both with reduced-dose CsA, or to (iii) MMF 3 g/day with standard-dose CsA [9]. All patients received corticosteroids with or without induction according to center practice. Randomization to the high everolimus trough concentration group (6–12 ng/mL) was stopped prematurely due to higher early mortality, and data from this group were not analyzed in detail. The primary efficacy endpoint was the composite efficacy failure (biopsy-proven acute rejection of ISHLT grade ≥ 3A, acute rejection episodes associated with hemodynamic compromise, graft loss/retransplant, death, and loss to followup) and the main secondary efficacy endpoint was the incidence rate of graft loss/retransplant, death, or loss to followup, both at month 12 [9].

2.2. Efficacy Results. According to the primary efficacy endpoints, everolimus was significantly more efficacious than azathioprine at month 6 aftertransplant when both agents were administered with standard-dose CsA (B253) [2], and noninferior when given with reduced-exposure CsA compared to MMF plus standard-exposure CsA at months 12 and 24 aftertransplant (A2310) [9] (Table 2). The German single-center observational study by Lehmkuhl et al. indicated that a low initial CsA target trough range of 200–250 ng/mL during the first month aftertransplant, subsequently downtitrated to achieve a reduction of 58% by month 12, is feasible without loss of immunosuppressive efficacy [10].

In B253, the incidences of graft loss and death were comparable between treatment groups [2]. In the A2310 trial, the combination of highly-exposure everolimus (target C0 6–12 ng/mL) with CsA and MMF was associated with increased mortality, leading to discontinuation of recruitment to that study arm. In the standard-exposure everolimus group, mortality was similar to the control arm only in the absence of induction therapy. Increased infection-related mortality was observed during the first three months aftertransplant in patients receiving standard-exposure everolimus in conjunction with antithymocyte globulin (Thymoglobulin) induction. Further subanalyses revealed an association of deaths in the everolimus group with the use of a left ventricular assist device (LVAD) beforetransplant, and that virtually all deaths in patients with LVAD and Thymoglobulin induction occurred in German centers. The German procedure for selecting highly urgent heart transplant recipients for preferred allocation results in a very high-risk population; for example, LVAD patients are only allocated to a donor very urgently in the event of technical failure, relapsing strokes, or LVAD infection. If these LVAD patients, often with specific risks such as concomitant infection, receive Thymoglobulin induction plus early introduction of a mTOR inhibitor, the intensity of immunosuppression can become supratherapeutic. In these patients, everolimus should not be initiated until wound healing is complete and any bacterial or fungal infections have been cleared. By month 24, the mortality rate in the A2310 study was similar in the everolimus and MMF groups (10.6% versus 9.2%, resp.). Other efficacy endpoints were also similar between the two treatment groups, consistent with earlier data from the A2411 trial in de novo heart transplant patients (Table 2).

2.3. Safety Profile. In most cases, the side effects of everolimus (e.g., dyslipidemia, elevated creatine kinase, acne, aphthous stomatitis, edema, pneumonia, proteinuria, leukopenia, and
Table 1: Clinical studies of everolimus versus azathioprine or mycophenolate mofetil (MMF) in de novo heart transplant recipients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Primary endpoint</th>
<th>Everolimus</th>
<th>Comparator</th>
<th>CsA C₀ target range (ng/mL) by month</th>
<th>Induction therapy</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>B253 [2]</td>
<td>24-month Multicenter Randomized</td>
<td>Composite efficacy failure at 6 months</td>
<td>Fixed-dose(^a) 1.5 mg/day ((n = 209)) 3.0 mg/day ((n = 211))</td>
<td>Azathioprine(^a) 1–3 mg/kg/day ((n = 214))</td>
<td>All 3 groups: l: 250–400 2–6: 200–350 7–24: 100–300</td>
<td>In individual centers only: ATG or muromonab-CD3</td>
<td>Prednisolone, initiated at 0.5–1.0 mg/kg/day, tapered to achieve 0.3–0.5 mg/kg/day by day 21 and ≥0.1 mg/kg/day by month 6</td>
</tr>
<tr>
<td></td>
<td>Double-blind for months 0–12, open-label for months 12–24</td>
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<tr>
<td>Lehmkuhl et al. 2007 [10]</td>
<td>12-month Single center Retrospective</td>
<td>Not applicable</td>
<td>Initial dose before transplant 0.75 mg, then mean 1.5–1.75 mg/day, and (C₀) 3–8 ng/mL ((n = 38))</td>
<td>MMF before transplant 1.0 g, then mean 1.5–2.5 g/day ((n = 18))</td>
<td>Everolimus versus MMF: l: 200–250, both groups 2: 175–200 versus 200–250 3–4: 150–175 versus 200–250 5–6: 100–150 versus 150–200 7–12: 80–120 versus 120–150</td>
<td>ATG 2.5 mg/kg/day on days 1 and 2</td>
<td>Initially, high-dose methylprednisolone, then prednisolone 1 mg/kg/day, tapered to achieve 0.1 mg/kg/day by month 12</td>
</tr>
<tr>
<td>A2411 [3]</td>
<td>12-month Multicenter Randomized</td>
<td>Noninferiority of renal function (calculated creatinine clearance at 6 months)</td>
<td>Initial dose(^a) 1.5 mg/day, (C₀) 3–8 ng/mL ((n = 92))</td>
<td>MMF(^a) 3.0 g/day ((n = 84))</td>
<td>Everolimus versus MMF: l: 200–350, both groups 2: 150–250 versus 200–350 3–4: 100–200 versus 200–300 5–6: 75–150 versus 150–250 7–12: 50–100 versus 100–250</td>
<td>Antithymocyte antibodies (68.4% of patients) or IL-2RA (25.9% of patients)</td>
<td>Prednisone, tapered to achieve ≥0.1 mg/kg/day by month 6 and 0.1–0.05 mg/kg/day from month 6 to 12</td>
</tr>
<tr>
<td>A2310 [9]</td>
<td>24 months Multicenter Randomized</td>
<td>Noninferiority of composite efficacy failure at 12 months IVUS substudy: change in mean MIT at 12 months</td>
<td>Initial dose(^a) 1.5 mg/day, (C₀) 3–8 ng/mL ((n = 282)) or 3.0 mg/day, (C₀) 6–12 ng/mL ((n = 168))</td>
<td>MMF(^a) 3.0 g/day ((n = 271))</td>
<td>Everolimus versus MMF: l: 200–350, both groups 2: 150–250 versus 200–350 3–4: 100–200 versus 200–300 5–6: 75–150 versus 150–250 7–12: 50–100 versus 100–250</td>
<td>Center-specific: No induction or Thymoglobulin or basiliximab</td>
<td>Yes, according to local practice</td>
</tr>
</tbody>
</table>

ATG: antithymocyte globulin; CsA: cyclosporine; IL-2RA: interleukin-2 receptor antibody; IVUS: intravascular ultrasound; MIT: maximum intimal thickness.

\(^a\)First dose administered within 72 hours after transplant surgery.
Due to their antiproliferative properties, mTOR inhibitors can impair wound healing after surgery [12]. Clinical evidence regarding an effect on wound healing in heart transplantation is mixed [5, 9, 13]. Randomized studies indicate an elevated incidence of pericardial and possibly pleural effusion (see Supplementary Table 1 in Supplementary Material available online at http://dx.doi.org/10.1155/2013/683964). In the A2310 study, pericardial effusions were most frequent with MMF at month 12, but rates of pericardial tamponade, pleural effusions, sternal and nonsternal wound healing complications, and wound infections were similar between groups [5, 9, 13] (Supplementary Table 1). The difference in pericardial effusions contributed to a higher overall rate of study drug discontinuation due to adverse events with everolimus versus MMF at 12 months (29.7% versus 19.0%) although this diminished by month 24 (33.3% versus 25.7%) [10]. The ongoing EVERHEART study (NCT01017029), which is being undertaken in a de novo heart transplant population randomized to receive everolimus immediately or with a delay of 4–6 weeks, includes pericardial effusion as a prespecified endpoint [14].

Viral infections were less frequent with everolimus versus MMF in the A2310 trial, largely accounted for by a lower rate of cytomegalovirus (CMV) infection in everolimus-treated patients (8.2% versus 20.5% with MMF at 12 months, \( P < 0.001 \); 9.3% versus 23.9% at month 24, \( P < 0.001 \)). These results substantiate similar findings in the A2411 study [5], in B253 study [2], and a recent pooled analysis [15]. The consistent reduction in CMV infection with everolimus versus azathioprine or MMF [2, 5, 9] is independent of CMV prophylaxis and donor/recipient serostatus [9]. Other viral infections such as herpes simplex virus, Epstein-Barr virus, polyoma virus, and herpes zoster virus may be lowered by everolimus, but studies have not been designed with these infections as predefined endpoints. Of note, although viral infections are reduced, bacterial or fungal infections may be more frequent with everolimus, and avoiding immunosuppression is critical to reduce this risk.

2.4. Renal Function. Neither the A2310 study [9] nor the A2411 trial [5] showed a renal benefit for everolimus versus MMF (Supplementary Table 2). Indeed, noninferiority of renal function for everolimus versus MMF was not shown in the A2310 study since the lower limit of the confidence interval was lower than the prespecified margin of −10 mL/min/1.73 m\(^2\) (the difference in mean eGFR was −5.55 mL/min/1.73 m\(^2\), 97.5% CI [−10.9, −0.2]) [9]. This was probably due to the absence of CsA dose reduction during the first month after transplant and subsequent nonadherence to targets for CsA reduction in the everolimus group. It is interesting to note that from month 1 to month 12, when CsA target levels were lower in everolimus-treated patients, the decline in eGFR was smaller with everolimus versus MMF (−8.6 versus −14.6 mL/min/1.73 m\(^2\), \( P = 0.009 \)) [9].

Converting maintenance heart transplant patients from a standard CNI regimen to everolimus with reduced CNI therapy can offer a significant improvement in renal function, as demonstrated in the randomized NOCTET study.
[6] and during single-center experience [16], even when administered at a low dose [17], although conflicting data exist [8]. CsA dose must be reduced stepwise compared to standard dosing in the presence of everolimus, which can be undertaken without loss of efficacy [18], or the CsA reduction is inadequate to protect renal function. In the event of CNI-related nephrotoxicity, early switch to a mTOR inhibitor appears advisable since the positive effects on renal function are more pronounced if conversion is performed in the first year, although no specific time limit has been established. In the SHIRAKISS trial of 34 maintenance patients with renal dysfunction who were between one and four years after transplant, conversion to everolimus with a 70% reduction in CsA exposure only improved renal function in patients without proteinuria at the time of conversion [8]. Patients with proteinuria continued to show renal deterioration despite the switch to everolimus therapy. The decision on timing needs to take into account the fact that CNI therapy may be necessary for the first nine months after heart transplantation. Most side effects in maintenance patients occur within six months after starting everolimus and may necessitate a temporary switch back to CNI therapy. In patients with steroid-resistant recurrent myocardial rejection, permanent reintroduction of low-dose CNI may be required.

There is widespread experience in German centers of CNI withdrawal and long-term CNI-free immunosuppression using everolimus in maintenance patients after heart transplantation. Stypmann et al. described a cohort of 60 patients switched to a CNI-free regimen in response to deteriorating renal function, recurrent rejection, or side effects under CNI-based therapy [19]. After 24 months, renal function had improved significantly (mean (SD) creatinine clearance (Cockcroft-Gault) 41.8 [22] mL/min versus 48.6 [21.8] mL/min at baseline, \(P < 0.001\)).

2.5. Cardiac Allograft Vasculopathy. The B253 study of everolimus versus azathioprine in de novo heart transplant patients first indicated that everolimus may inhibit the development of CAV [2]. Intravascular ultrasonography (IVUS) studies showed a significant reduction of the average increase of the maximal intimal thickness (MIT) from baseline to month 12 after transplant in patients receiving everolimus compared to azathioprine and a significantly lower incidence of CAV (defined as an increase in MIT \(\geq 0.5\) mm) (Table 3). These findings are highly relevant since MIT at 12 and 24 months after heart transplantation predicts subsequent major adverse cardiac events and death [21, 22]. In the A230 study, IVUS data at month 12 confirmed that the mean increase in MIT was smaller with everolimus than MMF, accompanied by a lower incidence of protocol-defined CAV (Table 3). All other predefined IVUS endpoints were also significantly in favor of everolimus [9]. This benefit was observed despite higher mean levels of total cholesterol in everolimus-treated patients [9].

According to ISHLT guidelines everolimus, sirolimus as tolerated, or MMF should be a part of the immunosuppression regimen after heart transplantation to reduce the onset and progression of CAV [23]. mTOR inhibition can be substituted for MMF or azathioprine in patients who develop CAV, although data are lacking regarding the effect of late conversion to mTOR inhibition on CAV progression.

2.6. Posttransplant Malignancy. mTOR inhibitors exert a direct antineoplastic effect by the inhibition of the phosphatidylinositol-3-kinase (PI3K) pathway and by sensitization of tumor cells to apoptosis via inhibition of the p53-induced p21 expression regulating abnormal cellular proliferation and differentiation [24]. A randomized, double-blind, phase 3 trial has demonstrated significantly better progression-free survival in patients with metastatic renal cell carcinoma who received everolimus compared to placebo (RECORD-1) [25, 26]. Everolimus is licensed for the treatment of advanced renal cell carcinoma and for advanced breast cancer and is currently under investigation for the management of other types of malignancy.

There are case reports describing regression of Kaposi's sarcoma [27] and malignant neoplasia [28, 29] in kidney transplant recipients following conversion from CNI to everolimus, and Tiberio et al. have described significant regression of cardiac rhabdomyoma in a patient receiving everolimus [30]. Kusuki et al. reported a case of successful management of diffuse large B-cell lymphoma 29 months after cardiac transplantation in a 47-month-old boy using minimized CsA in combination with everolimus following rituximab treatment and chemotherapy [31]. Conversion from CNI to everolimus therapy to control malignancy following heart transplantation would seem a reasonable therapeutic approach, particularly for Kaposi's sarcoma, non-melanoma skin cancer, and renal cell carcinoma [32] but robust data are lacking. The ongoing multicenter, randomized CERTICOEUR trial (NCT00799188) is comparing the development of new skin cancers in 159 heart transplant patients suffering recurrent skin cancer receiving everolimus and reduced or discontinued CNI therapy versus standard CNI therapy. Importantly, evidence is also growing for a protective role of mTOR inhibitors on the risk of developing new malignancies or nonskin solid tumors following kidney transplantation [32]. Data are awaited in heart transplant recipients.

2.7. Pediatric Heart Transplant Recipients. Minimization of steroids and exposure to CNIs are especially vital in children to reduce the risk of metabolic disorders, renal dysfunction, and cancer. While early withdrawal of steroids is a well-established strategy in pediatric transplant recipients, there is only limited experience with-reduced-CNI or CNI-free regimens [33, 34]. Everolimus is not currently licensed in children and its use in pediatric heart transplant patients is largely restricted to high-volume centers [35]. There are no randomized trials. Behne-Hall et al. have published their experience of switching from CNI therapy to everolimus in 28 children with poor renal function (eGFR < 75 mL/min/1.73 m²) at a median of 9.81 years following heart transplantation [36]. All patients were also receiving azathioprine or MMF (those on azathioprine were converted to MMF before the switch to everolimus). In this series, median
Everolimus acts synergistically with CsA, such that CsA exposure should be reduced in the presence of everolimus. Lehmkuhl et al. reported a reduction in mean CsA trough concentration of 47% at two weeks and 58% at 12 months after transplantation [10] compared to standard dose. A drug-drug interaction between everolimus and tacrolimus, by which everolimus decreases tacrolimus oral bioavailability in a dose-dependent manner [44], means that tacrolimus dose reductions should be smaller than those required for CsA, particularly during the early posttransplant phase, to avoid rejection.

In CNI-free regimens, everolimus should be used in combination with mycophenolic acid.

Everolimus has a shorter half-life than sirolimus (28 hours versus 62 hours) with a more rapid time to steady state (4 days versus 5–7 days) and as a result does not require a loading dose [45–50] (Supplementary Table 3). It is administered twice daily together with the concomitant immunosuppressive medication. Stable trough blood levels (3–8 ng/mL) can be obtained after approximately 3–7 days and should be monitored 1–2 times a week initially, then weekly for the following two months, and every 2–4 weeks thereafter. If the everolimus dose or concomitant medication is changed, the frequency of monitoring should be increased until steady state is achieved. The daily dose should not exceed 3.0 mg even if the target trough concentration is not achieved other than in a very few instances (e.g., in patients receiving comedication that induces enzymatic induction), when a higher dose may be appropriate for a limited period.

### 4. Selection of Patients for Everolimus Therapy

#### 4.1. De Novo Heart Transplant Recipients

Unless there are special considerations to take into account, all de novo heart transplant patients can be considered potential candidates for everolimus-based immunosuppression. Caution should be exercised in certain categories of patients, however, such as those at risk of severe proteinuria, poor wound healing, or patients who have uncontrolled severe hyperlipidemia or

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**Table 3: Results of intravascular ultrasound (IVUS) substudies in randomized trials of everolimus with reduced-exposure cyclosporine.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MMF</th>
<th>Everolimus 1.5 mg</th>
<th>P value</th>
<th>Azathioprine</th>
<th>Everolimus 1.5 mg/3.0 mg</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>101</td>
<td>88</td>
<td></td>
<td>72</td>
<td>70/69</td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td>—</td>
<td>—</td>
<td></td>
<td>60</td>
<td>45/44</td>
<td></td>
</tr>
<tr>
<td>Mean change in MIT from baseline, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>0.07 ± 0.11</td>
<td>0.03 ± 0.05</td>
<td>&lt;0.00</td>
<td>0.10</td>
<td>0.04/0.03</td>
<td>0.01/0.003</td>
</tr>
<tr>
<td>24 months</td>
<td>—</td>
<td>—</td>
<td></td>
<td>1</td>
<td>0.15</td>
<td>0.07/0.06</td>
</tr>
<tr>
<td>Patients with CAV, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12 months</td>
<td>26.7</td>
<td>12.5</td>
<td>0.018</td>
<td>52.8</td>
<td>35.7/30.4</td>
<td>0.045/0.01</td>
</tr>
<tr>
<td>24 months</td>
<td>—</td>
<td>—</td>
<td></td>
<td>58.3</td>
<td>33.3/45.5</td>
<td>0.017/n.s.</td>
</tr>
</tbody>
</table>

CAV: cardiac allograft vasculopathy, defined as a change in MIT ≥ 0.5 mm as assessed by intravascular ultrasound (IVUS); MIT: maximal intimal thickness; MMF: mycophenolate mofetil.
Everolimus only with special care

Reducing CsA exposure to a minimum, monitoring urine electrophoresis and proteinuria, and stopping everolimus in the event of proteinuria > 1 g/day and/or signs of new glomerular damage on urine electrophoresis

Risks for wound healing disorders (diabetes mellitus, obese patients, high steroid exposure, and ventricular assist device)

Delay initiation of everolimus until completion of wound healing and resolution of any bacterial or fungal infection

Uncontrolled severe hyperlipidemia

Delay initiation of everolimus until serum lipids have been controlled
Always administer everolimus in combination with lipid-lowering therapy for example, fluvastatin

Everolimus not appropriate

Avoid antilymphocyte antibodies for induction in patients with elevated risk for early postoperative infection
Everolimus may be initiated after completion of wound healing and resolution of any bacterial or fungal infection

Latent bacterial or fungal infections

Everolimus may be unsuitable in individual cases based on benefit/risk assessment

High probability of reoperation or necessity for additional surgery in the initial phase

Considering late initiation of everolimus to avoid the need to switch immunosuppressive regimen during a critical period

GFR < 40 mL/min/1.73 m² if slope shows an ongoing deterioration of renal function

Delay initiation of everolimus
Everolimus may be initiated if CNI exposure requires marked reduction

* Initiation within 72 hours after transplantation.
CAV: cardiac allograft vasculopathy; CNI: calcineurin inhibitor; CsA: cyclosporine; GFR: glomerular filtration rate; LVAD: left ventricular assist device.
with stepwise reductions in CNI dose. Once the everolimus trough concentration is in the range 3–8 ng/mL, the CNI is withdrawn. In patients receiving everolimus with CNI and a CNI-free regimen is sought, MMF can be introduced at a dose of 1.0–1.5 g b.i.d. with stepwise withdrawal of CNI starting approximately one week later. In the early period after CNI withdrawal, close observation of allograft function by echocardiography and endomyocardial biopsy coupled with monitoring of everolimus and mycophenolic acid trough concentrations is very important. Patients who are receiving azathioprine and CNI also need a stepwise approach to CNI discontinuation. First, azathioprine is replaced by everolimus with a simultaneous reduction in CNI dose. Azathioprine is discontinued as soon as adequate everolimus trough concentrations are reached. In a second step, several weeks later, the CNI dose is reduced stepwise while mycophenolic acid is introduced. Close monitoring of allograft function is again mandatory.

5. **Drug Interactions**

Everolimus interacts with cytochrome P450 (CYP) enzymes 3A4, 3A5, and 2C8 [53]. Drugs which influence the CYP3A pathway, in particular, affect everolimus metabolism. Concomitant administration of some CYP3A4 inhibitors (e.g., azithromycin, erythromycin, ketoconazole, and itraconazole) induces 18–74% reduction in everolimus clearance, resulting in an increased maximum concentration and prolonged everolimus half-life, while others (e.g., calcium channel blockers, quinolones, and trimethoprim-sulfamethoxazole) have no relevant effect. CYP3A inducers (rifampicin, phenytoin, and carbamazepine) decrease everolimus blood concentration to varying degrees. CsA is metabolized via the CYP3A isoenzyme system and has been shown in single-dose healthy volunteer studies to increase everolimus blood concentration [54] but the steady-state pharmacokinetics of CsA are not influenced by coadministration of everolimus. A reduction in CsA exposure is necessary to avoid CNI-related nephrotoxicity in combination with everolimus.

The combination of tacrolimus and everolimus for prophylaxis of acute rejection after heart transplantation is administered in selected patients in some German centers, although this remains off-label use. There is evidence from kidney transplantation that co-administration of everolimus with tacrolimus reduces tacrolimus exposure [44]. Therefore, tacrolimus dose reduction is considered necessary, although to a lesser extent than for CsA. Tacrolimus does not influence everolimus blood levels, such that higher doses of everolimus are required than those in CsA-treated patients to maintain therapeutic blood levels of everolimus [55]. Tacrolimus is as effective as CsA in combination with everolimus after heart transplantation, and the incidence of serious hypertriglyceridemia is similar [56].

6. **Management of Adverse events**

Everolimus trough blood concentrations in the range 3–8 ng/mL are well tolerated and associated with a low incidence of side effects, but higher levels are not well tolerated. If everolimus trough concentration exceeds 10 ng/mL, an immediate dosage reduction is likely to be necessary since in addition to a high incidence of everolimus-specific side effects there is an increased risk of over-immunosuppression. Most adverse events are not lifethreatening and are responsive to treatment. In clinical practice, preventive measures, optimal screening, and management of side effects should be routine. Experienced-based algorithms may help to avoid the need for everolimus discontinuation.

Management strategies for specific types of everolimus-related adverse events in heart transplant recipients have been discussed in detail elsewhere [4, 11] and key aspects are summarized in Table 5. Routine comedication with lipid-lowering medication is essential in heart transplant patients receiving a mTOR inhibitor. Statin therapy is standard, but in view of the known potential for drug-drug interactions between drugs that affect CYP3A metabolism of everolimus, agents that do not interact with CYP450 should be selected, such as pravastatin, fluvastatin, or fibrates.

7. **Discontinuation of Everolimus**

Discontinuation of everolimus in heart transplant recipients is associated with a decline in renal function [57] but withdrawal or temporary interruption may be necessary if severe everolimus-related side effects cannot be managed or if surgery is planned. Everolimus can be replaced by MMF using a stepwise switch. In the event of surgery, this stepwise process should be timed to ensure that everolimus is withdrawn at least seven days before the operation is scheduled. Since adequate blood concentration of MMF requires several days to achieve, overlap of everolimus and MMF administration is advisable for approximately four days. The CNI blood level is likely to increase during everolimus withdrawal and both blood concentrations and renal function should be monitored closely during and after discontinuation. After the side effects have resolved or wound healing is complete, reintroduction of everolimus can be considered.

In patients receiving CNI-free immunosuppression, the risk of postoperative infection must be carefully balanced with the risk of renal function impairment associated with the reintroduction of CNI. For elective major thoracic, abdominal, and retroperitoneal surgery, stepwise reintroduction of CNI in combination with MMF and withdrawal of everolimus is appropriate. This switch should be undertaken approximately two weeks before surgery with reconversion to a CNI-free regimen as soon as wound healing is completed.

8. **Conclusions**

The efficacy of everolimus at a trough concentration of 3–8 ng/mL in combination with reduced-exposure CsA is noninferior to MMF plus full-exposure CsA up to two years after heart transplantation. Data regarding concomitant use of everolimus with tacrolimus remain limited. The side effects which are potentially associated with the use of
Table 5: Overview of selected everolimus-associated adverse events.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Comment</th>
<th>Prevention/intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>Comedication with lipid-lowering medication is mandatory (statin not interacting with CYP450 e.g. fluvastatin, or fibrates)</td>
<td></td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>In unexplained cytopenia (white blood cells, red cells, platelets), everolimus may be the cause and dose reduction or temporary cessation may be indicated</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>Improves within a few weeks using local treatment</td>
<td></td>
</tr>
<tr>
<td>Aphthous stomatitis</td>
<td>Local treatment is effective</td>
<td></td>
</tr>
<tr>
<td>Angioneurotic edema</td>
<td>Discontinue ACE inhibitor comedication</td>
<td></td>
</tr>
<tr>
<td>Creatine kinase (CK) elevation</td>
<td>May be related to everolimus overexposure or/and to comedication of statin therapy</td>
<td></td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>May reflect physiological tubular proteinuria due to mTOR inhibition, which is reversible and without clinical relevance as it does not reflect damage to renal tissue Proteinuria &gt; 1 g/day indicates a glomerular process and may be due to an everolimus-associated event</td>
<td></td>
</tr>
<tr>
<td>Increased proteinuria</td>
<td>Concomitant prescription of ACE inhibitor or angiotensin-receptor blockers may reduce the incidence of new onset proteinuria As proteinuria &lt; 1 g/day does not exclude glomerular damage, urine protein electrophoresis can be performed to detect glomerular proteins</td>
<td></td>
</tr>
<tr>
<td>Noninfectious pneumonia</td>
<td>More likely to occur during sirolimus treatment in cancer patients</td>
<td></td>
</tr>
<tr>
<td>Impaired wound healing</td>
<td>Elevated risk early postoperatively in high-risk patients (e.g., diabetes, LVAD, redo surgery, and high-dose steroids) due to antiproliferative properties of mTOR inhibitors Delayed onset of everolimus after transplant surgery, or temporary interruption during subsequent major surgery, may be helpful. In the event of minor local surgery in low-risk patients, everolimus therapy can be continued</td>
<td></td>
</tr>
<tr>
<td>Pericardial/pleural effusion</td>
<td>Elevated incidence early after heart transplantation Manageable by frequent monitoring with echocardiography/sonography, symptomatic diuretic treatment, and drainage on demand</td>
<td></td>
</tr>
</tbody>
</table>

ACE: angiotensin converting enzyme; LVAD: left ventricular assist device; MMF: mycophenolate mofetil; mTOR: mammalian target-of-rapamycin inhibitor.

mTOR inhibitors do not represent a major threat in the clinical situation. In addition, when administered in combination with MMF, everolimus offers the option of CNI-free immunosuppression in selected patients beyond the first year after heart transplantation.

Recent concerns about early increased mortality in the everolimus groups of the A2310 study can be explained by overimmunosuppression in patients with LVAD before transplantation, which arose predominantly from a country-specific effect in Germany. If patients with LVAD and specific risks such as infection receive Thymoglobulin induction plus early mTOR inhibition, the intensity of immunosuppression accumulates to an intolerable level with an associated increase in infection-related mortality. Such patients should not receive everolimus before wound healing is completed and any bacterial or fungal infection has been cleared.

The most important benefit of everolimus therapy in heart transplantation may be that its dual mode of action—prevention of acute allograft rejection coupled with suppression of growth factor-driven smooth muscle cell proliferation—combines immunosuppressive potency with the reduction of de novo CAV disease. The significant reduction in CMV infection in everolimus-treated patients may also contribute to the minimization of intimal vascular changes. For the first time, the A2310 study has shown superiority for everolimus versus MMF in all relevant IVUS parameters [9], in accordance with earlier subanalyses from the B253 study comparing everolimus with azathioprine [2]. Of note, everolimus was
initiated early (i.e., within the first 72 hours after transplantation) in both trials. This may be an important detail as many preconditioning events which predispose to CAV start at the time of heart transplantation.

Careful patient selection and individualized immunosuppression are a key to achieving optimal outcomes after heart transplantation. Due to its potential to inhibit progression of CAV and to reduce CMV infection, everolimus should be initiated as soon as possible after heart transplantation and be included in standard immunosuppressive regimens if special care is applied in specific patient types and unsuitable patients are excluded (Table 5). Immediate and adequate reduction of CsA exposure is mandatory from the start of everolimus therapy. The findings of the MANDELA and SCHEDULE trials may, in the future, support adoption of CNI-free immunosuppression with combined everolimus and MMF therapy beyond six months after heart transplantation, and results of these trials are awaited with interest.

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