

Review article

An overview of the efficacy and safety of everolimus in adult solid organ transplant recipients

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ABSTRACT

As the risk of graft loss due to acute rejection has declined, the goal of post-transplant management has switched to long-term preservation of organ function. Minimizing calcineurin inhibitor (CNI)-related nephrotoxicity is a key component of this objective. Everolimus is a mammalian target of rapamycin inhibitor/proliferation-signal inhibitor with potent immunosuppressive and anti-proliferative effects. It has been widely investigated in large randomized clinical studies that have shown it to have similar anti-rejection efficacy compared with standard-of-care regimens across organ transplant indications. With demonstrated potential to facilitate the reduction of CNI therapy and preserve renal function, everolimus is an alternative to the current standard-of-care CNI-based regimens used in de novo and maintenance solid organ transplantation recipients.

Here, we provide an overview of the evidence from the everolimus clinical study program across kidney, liver, heart, and lung transplants, as well as other key data associated with its use in CNI reduction strategies in adult transplant recipients.

1. Introduction

Solid organ transplantation is an effective treatment option for hundreds of thousands of patients worldwide [1]. In addition to advancements in organ preservation procedures and peri-and post-operative management, the use of immunosuppressive drugs has resulted in improved patient and allograft survival [2].

The modern immunosuppressive era came with the introduction of the calcineurin inhibitor (CNI) cyclosporine in the early 1980s, which revolutionized short-term outcomes after kidney transplantation [3] and remained a cornerstone of immunosuppression in transplantation for decades [4]. The 1990s saw the introduction of a number of important agents, including the CNI tacrolimus, which in combination with improving clinical care resulted in 1-year graft survival exceeding 90% in kidney transplantation [3]. The use of tacrolimus has increased steadily since its introduction and it is now the dominant CNI used in

clinical practice, although the strengths of both cyclosporine and tacrolimus are often utilized depending on individual patient risk [5]. Despite these advances in short-term graft survival, long-term outcomes remain unchanged.

In kidney transplant recipients, a major cause of graft failure is the development of renal damage, to which CNI use is a contributor. Long-term use of CNIs is associated with nephrotoxicity [5,6], neurotoxicity [7,8], cardiovascular (CV) disease and metabolic abnormalities [9,10], and malignancy [11–13]. Among other solid organ transplant recipients, the incidence of post-transplant kidney diseases is high across the different organ types (heart, 20%–30%; liver, 46%–61%; lung, 5%–60%), and this is mostly associated with CNI toxicities [14,15]. Both acute renal failure and chronic kidney disease contribute to increased morbidity and premature mortality [15].

As the risk of graft loss due to acute rejection in the short term has declined since the introduction of CNIs, the goal of management has

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<https://doi.org/10.1016/j.trre.2021.100655>

switched to long-term preservation of organ function. Immunosuppressive strategies are being developed that permit early CNI reduction or withdrawal, potentially leading to a reduction in CNI-related nephrotoxicity and other adverse events (AEs), without compromising acute rejection rates.

Everolimus (Certican®/Zortress®, Novartis) is a mammalian target of rapamycin (mTOR) inhibitor/proliferation-signal inhibitor with potent immunosuppressive and anti-proliferative effects. The immunosuppressive activity of mTOR inhibitors is exerted through blocking the cell division of activated T cells [16,17]. As mTOR is a serine/threonine kinase that regulates cell cycle progression and proliferation signaling pathways in response to growth factors and nutritional conditions, mTOR inhibitors have anti-proliferative effects beyond the immune system [12].

Everolimus is a semi-synthetic derivative of naturally occurring rapamycin and has been widely investigated in large randomized clinical studies that have shown it to be highly effective in preventing acute rejection in kidney, liver, heart, and lung transplant recipients [18–23]. This has allowed its registration across several countries for clinical use in combination with CNIs (cyclosporine in kidney and heart transplant recipients and tacrolimus in liver transplant recipients). In addition, several studies have demonstrated the potential for everolimus use to reduce or withdraw CNI therapy and preserve renal function [24–30], which is an important factor in the amelioration of CV events [31]. The anti-proliferative effects of mTOR inhibitors may also provide other benefits over CNIs, for example fewer de novo malignancies, a reduced incidence of viral infections, and reduced progression of cardiac allograft vasculopathy in heart transplant recipients [27,32–34].

This review focuses on evidence from the everolimus clinical study program across kidney, liver, heart, and lung transplants, as well as other key data associated with its use in CNI reduction and withdrawal strategies in adult transplant recipients.

2. Pharmacokinetic properties of everolimus

Everolimus was developed to improve the pharmacokinetic (PK) characteristics of its analog, rapamycin, also known as sirolimus [35,36]. The introduction of a hydroxyethyl moiety at position 40 alters the chemical properties and PK of everolimus compared with sirolimus. Everolimus is more polar and hydrophilic [16,18,37], exhibits a 60% higher bioavailability, and reaches a steady state faster than sirolimus (4 days vs 5–7 days) with a shorter half-life (28 vs 62 h) following oral

administration [36,38,39]. As a result of this shorter half-life, everolimus is dosed twice daily, which facilitates better dose adjustment and improved maintenance of target trough concentrations (C_0) compared with sirolimus [36,40].

The PK of everolimus has been reviewed previously [35,41]. In summary, everolimus is rapidly absorbed, and peak concentrations are reached after 1–2 h [42,43]. Steady-state peak and trough concentrations, as well as overall bioavailability as measured by area under the concentration-time curve (AUC), are proportional to dosage. The absorption rate of everolimus is slowed by a high-fat meal, which delays the time to reach peak concentration (C_{max}) by a median of 1.25 h, decreases C_{max} by 60%, and reduces AUC by 16% [42].

Everolimus has a narrow therapeutic index and therefore routine therapeutic monitoring is recommended to guide dosing of individual patients to achieve C_0 3–8 ng/mL when used in combination with CNIs [41,44]. Concomitant administration of cyclosporine with everolimus has been observed to boost everolimus blood levels by 2.7-fold, likely due to inhibition of everolimus metabolism by cyclosporine [45]. The recommended starting dose of everolimus when co-administered with cyclosporine is 0.75 mg twice daily [44]. A minimal drug interaction has been observed with tacrolimus on everolimus, so the starting dose of everolimus when combined with tacrolimus needs to be at least double that used when combined with cyclosporine, in order to achieve C_0 of >3 ng/mL in the first two weeks [46,47].

3. Therapeutic efficacy of everolimus-based regimen in adult solid organ transplantation

3.1. Evidence in kidney transplantation

Early studies leading to the approval of everolimus suggested that a dosing strategy consisting of concentration-controlled everolimus with $C_0 > 3$ ng/mL in combination with reduced-exposure CNI (rCNI) provides adequate immunosuppression while minimizing nephrotoxicity [20,21,26,48]. This section describes efficacy and renal function outcomes from key clinical studies further investigating the use of everolimus to reduce CNI exposure in the de novo and maintenance settings (Table 1).

3.1.1. Anti-rejection efficacy

Early head-to-head Phase III studies in de novo kidney transplant recipients (A2309 [NCT00251004] and A1202 in Japanese patients

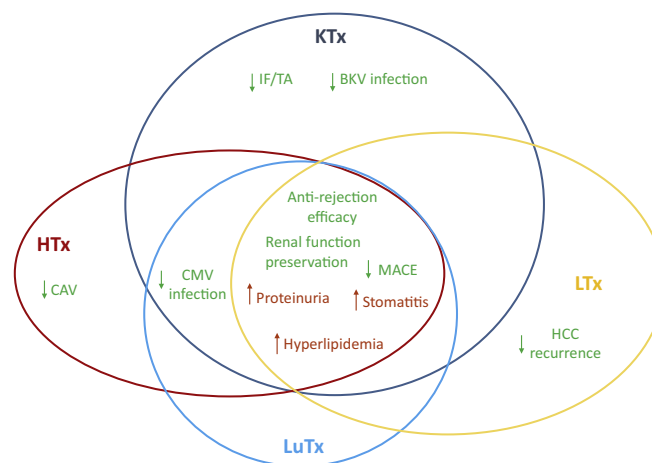


Fig. 1. Clinical implication of everolimus therapy in solid organ transplantation, based on results from key everolimus studies.

Upward arrow indicates the higher incidences and downward arrow indicates the lower incidences compared with control. Green text = possible benefits; Red text = possible limitations.

BKV, BK virus; CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus; HCC, hepatocellular carcinoma; HTx, heart transplantation; IF/TA, interstitial fibrosis and tubular atrophy; KTx, kidney transplantation; LTx, liver transplantation; LuTx, lung transplantation; MACE, major cardiac adverse events.

Table 1

Key clinical studies of everolimus in the context of reduced CNI exposure in kidney transplant recipients Findings of statistical significance highlighted in bold.

Study	Immunosuppressive regimen base	Month (M) of follow-up	Efficacy failure %	Renal function (mL/min/1.73 m ²)
De novo studies (time of EVR initiation post-transplant); number of patients (n)				
A2309 (≤24 h) n=833 [27, 70]	EVR (C ₀ 3–8 ng/mL) + rCsA	M12 M24	25.3 ^a 32.9 ^a	56.3 52.2
	EVR (C ₀ 6–12 ng/mL) + rCsA	M12 M24	21.9 ^a 26.9 ^a	55.0 49.4
	MPA + sCsA	M12 M24	24.2 ^a 27.4 ^a	54.4 50.5
A1202 (≤24 h) n=122 [49]	EVR (C ₀ 3–8 ng/mL) + rCsA	M12	11.5 ^a	62.1
	MMF + sCsA	M12	11.5 ^a	56.3
CERTES/LATAM (≤24 h) n=170 [50]	EVR (C ₀ 3–12 ng/mL) + CsA (withdrawal by M4–6)	M12	18.9 ^b	68.3
	EVR (C ₀ 3–12 ng/mL) + rCsA	M12	17.5 ^b	63.6
TRANSFORM (≤24 h) n=2037 [58]	EVR (C ₀ 3–8 ng/mL) + rCNI (CsA or TAC)	M12 M24	14.4 ^c 18.0 ^c	53.3 52.6
	MPA + sCNI (CsA or TAC)	M12 M24	13.0 ^c 17.3 ^c	54.5 54.9
ATHENA (≤24 h) n=655 [56]	EVR (C ₀ 3–8 ng/mL) + TAC	M12	13 ^d	61.9
	EVR (C ₀ 3–8 ng/mL) + CsA	M12	24.6 ^d	60.9
	MPA + TAC	M12	9.8 ^d p<0.001 (EVR/CsA vs MPA/TAC)	68.3 p<0.001 (both EVR arms vs MPA/TAC)
Maintenance studies (time of EVR conversion post-transplant); number of patients (n)				
ASCERTAIN (>6 months) n=394 [60]	sCNI-based regimen (TAC or CsA)	M24	8.9 ^b	46.0 ^f
	EVR (C ₀ 8–12 ng/mL) + CNI withdrawal (withdrawal when EVR C ₀ reached)	M24	13.4 ^b	48.0 ^f
	EVR (C ₀ 3–8 ng/mL) + rCNI	M24	11.8 ^b	46.6 ^f
CENTRAL (7 weeks) n=202 [63, 66]	sCsA + MPA	M12 M12–36	12.0 ^b 6.7 ^b	47.8 ^f 46.1 ^f
	EVR (C ₀ 6–10 ng/mL) + MPA (CsA withdrawal; overnight withdrawal)	M12	28.7 ^b p=0.005 sCsA/MPA vs EVR/MPA (M12)	51.2 ^f
		M12–36	3.3 ^b	48.2 ^f
ZEUS (4.5 months) n=503 [61, 62]	sCsA + MPA	M12 M60	16 ^e 24.0 ^e	61.9 60.9
	EVR (C ₀ 6–10 ng/mL) + MPA (CsA withdrawal; stepwise withdrawal over a maximum of 4 weeks)	M12 M60	19 ^e 31.2 ^e	71.8 p<0.0001 sCsA/MPA vs EVR/MPA (M12) 66.2 p<0.001 sCsA/MPA vs EVR/MPA (M60)
ELEVATE (10–14 weeks) n=715 [64]	EVR (C ₀ 6–10 ng/mL) + MPA	M12	6.1 ^c	64.1
	(CNI withdrawal; overnight or stepwise over 1 week)	M24	8.0 ^c	62.5
	sCNI therapy (TAC or CsA) + MPA	M12 M24	3.8 ^c 4.5 ^c	60.4 57.4 p=0.005 (EVR/MPA vs CsA/MPA)

Efficacy failure is the composite endpoint consisting of: ^aTreated BPAR, graft loss, death, or loss to follow-up; ^bBPAR, graft loss, death, or loss to follow-up; ^cTreated BPAR, graft loss, or death; ^dBPAR, graft loss or death; ^eBPAR, graft loss, death, loss to follow-up, discontinuation due to lack of efficacy or toxicity, or conversion to another regimen.

Renal function: mean estimated GFR (using MDRD, Nanvikell or Cockcroft-Gault formulas); ¹Calculated GFR.

BPAR, biopsy-proven acute rejection; CNI, calcineurin inhibitor; CsA, cyclosporine; C₀, trough level; EVR, everolimus; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; MMF, mycophenolate mofetil; MPA, mycophenolic acid; rCNI, reduced-exposure CNI; rCsA, reduced-exposure CsA; sCNI, standard-exposure CNI; sCsA, standard-exposure CsA; TAC, tacrolimus.

[NCT00658320]) comparing everolimus with reduced-exposure cyclosporine (r-cyclosporine) to a standard-of-care regimen containing standard-exposure cyclosporine (s-cyclosporine) reported non-inferiority of composite efficacy failure [27,49]. In the Phase III studies CERTES (NCT00154284) and LATAM (NCT00170807), comparable rates of efficacy failure have been observed with everolimus-facilitated cyclosporine reduction and withdrawal approaches [50], (Table 1).

With the emergence of tacrolimus as the standard-use CNI, clinical study protocols have evolved to evaluate the effect of everolimus in combination with tacrolimus and to establish optimal everolimus-facilitated tacrolimus reduction. Early Phase III studies of this era established the efficacy and tolerability of everolimus-based regimens with reduced-exposure tacrolimus (r-tacrolimus) in de novo kidney transplant recipients [51,52]. Additional studies also found that everolimus initiation at a dose of 1.5 mg twice daily in combination with r-tacrolimus is needed to maintain everolimus C₀ levels of 3–8 ng/mL for regimen efficacy [53,54]. The most recent de novo studies to report on the use of everolimus-facilitated r-tacrolimus regimens are TRANSFORM (Phase IV) and ATHENA (Phase III) [55,56].

TRANSFORM (NCT01950819), the larger of these studies with >2000 patients, investigated everolimus (C₀ 3–8 ng/mL) + rCNI (cyclosporine or tacrolimus) versus MPA + standard CNI (sCNI) [55]. In

consideration of pharmacokinetic actions, the starting dose of everolimus was 1.5 mg/day in combination with cyclosporine and 3 mg/day in combination with tacrolimus, in both cases the dose was then adjusted to target the determined C₀ throughout the study [55]. The everolimus + rCNI regimen was non-inferior to the MPA + sCNI regimen for the primary endpoint (a binary composite endpoint of treated BPAR or estimated glomerular filtration rate [eGFR] 50 mL/min per 1.73 m²) up to Month 24, with an incidence of 47.9% versus 43.7% respectively. This was supported by the key secondary efficacy endpoint (treated BPAR, graft loss, or death – see Table 1) and demonstrated that everolimus-facilitated tacrolimus or cyclosporine reduction is a valid alternative to standard-of-care therapy comprising MPA with sCNI [55,57,58]. In addition, the incidence of de novo DSA was lower in the everolimus + rCNI arm (12.3% vs 17.6%) among on-treatment patients [58].

In the ATHENA study (NCT01843348), 612 patients were randomized to receive everolimus (C₀ 3–8 ng/mL) + CNI (tacrolimus or cyclosporine) versus MPA + tacrolimus as the standard-of-care comparator. At 12 months of follow-up, composite efficacy failure (BPAR, graft loss, or death) was similar between the everolimus + tacrolimus and MPA + tacrolimus treatment arms, however there was a significant difference for everolimus + cyclosporine versus MPA + tacrolimus, mainly driven by a higher incidence of BPARs, which were largely graded as mild [56].

While the majority of de novo studies were carried out in patients

with low-medium immunological risk, a recent single-center, retrospective cohort analysis suggests that similar clinical outcomes may be obtained with everolimus + tacrolimus-based regimens in hyposensitized kidney transplant recipients [59].

In the maintenance setting, several Phase III randomized studies, including ASCERTAIN (NCT00170846), ZEUS (NCT00154310), CENTRAL (NCT00634920), and ELEVATE (NCT01114529) in Table 1, have examined outcomes for everolimus-based regimens, with conversion to everolimus occurring at various time points, ranging from 7 weeks to >6 months after transplantation [60–66]. Many of these evaluated the effect of everolimus on renal function as a primary endpoint, and are discussed in further detail in the next section (Section 3.1.2). In terms of immunosuppressive efficacy, conversion to everolimus-based CNI reduction regimens or everolimus-facilitated CNI withdrawal demonstrated similar efficacy to standard CNI regimens for up to 5 years of follow-up [62]. The CENTRAL study showed significantly higher rates of BPAR in the everolimus + CNI withdrawal arm, however these were mostly mild and did not adversely affect long-term graft function or survival [63,66]. In a retrospective single-center study of 126 patients recruited to the ZEUS study and another randomized study, an association between everolimus and risk of development of DSA and antibody-mediated rejection was detected [67]. However, differences between the two studies (e.g. the study populations, time of everolimus conversion, and the overall strategy) mean that the results are difficult to interpret [68].

In summary, everolimus-based CNI reduction has demonstrated effective immunosuppression when initiated at the time of kidney transplantation or in the maintenance setting. Drug discontinuation rates were generally higher with everolimus-based versus CNI-based regimens, although the different pattern of AEs observed with everolimus (see section 4 for further discussion of tolerability and AEs of interest reported with everolimus in key clinical studies) may have lowered the threshold for discontinuation of randomized treatment in the everolimus treatment arms. DSA after conversion to everolimus has also been observed in some studies.

3.1.2. Renal function

Minimizing CNI exposure is a key component of maintaining long-term patient outcomes. As previously noted, long-term CNI exposure has been associated with nephrotoxicity and increased risk of cardiovascular disease and malignancy [5,6,10,11,13]. In this section we discuss the effect of everolimus-facilitated CNI reduction on renal function (refer to Section 4 for further discussion of tolerability and AEs).

In the de novo setting, several clinical studies, including A2102 and CERTES/LATAM, have demonstrated maintained renal function with everolimus-based CNI reduction regimens for up to 12 months of follow-up [50,52,69]. In contrast to this, the recently published ATHENA study failed to demonstrate non-inferiority of renal function for the everolimus + CNI treatment arms versus the MPA + tacrolimus treatment arm at 12 months of follow-up. CNI levels, however, were consistently above protocol and a post hoc analysis considering only patients whose CNI levels were consistently within the target range found no significant difference in renal function between treatment arms, therefore highlighting the importance of adhering to target trough levels of CNI [56].

Considering de novo studies with follow-up beyond 12 months, the A2309 study demonstrated non-inferior renal function across treatment arms (everolimus + r-cyclosporine vs MPA + s-cyclosporine) up to Month 24 [27,70]. Consistent with these findings, the TRANSFORM study also demonstrated comparable renal function across the everolimus + rCNI and MPA + sCNI treatment arms. The absence of renal function benefit with the everolimus + rCNI regimen versus MPA + sCNI in TRANSFORM can be partly explained by a large proportion of patients who did not attain the recommended CNI target range in the everolimus + rCNI arm, reiterating the importance of adhering to target CNI trough levels [57]. Of note, a subgroup analysis of TRANSFORM indicated that

donor type may influence renal outcomes; for living donor and standard-criteria deceased donor subgroups, the eGFR in both the everolimus + rCNI and MPA + sCNI treatment arms was above or near the clinically significant level of 60 mL/min/1.73 m² at Month 24, yet for the extended-criteria donor subgroups, the eGFR was <45 mL/min/1.73 m² at Month 24 [58].

In the maintenance setting, several studies have investigated renal outcomes across different time points of conversion to everolimus-based regimen [60,62–65]. In the ASCERTAIN study (mean time to everolimus conversion of 5.6 years), stable renal function was reported across treatment regimens (everolimus + CNI withdrawal vs everolimus + rCNI vs sCNI) at Month 24. Despite the lack of renal benefit observed in the everolimus treatment arms in the overall population, a post hoc multivariate analysis indicated that patients with baseline creatinine clearance (CrCl) >50 mL/min may benefit from a change in therapy more than 6 months after renal transplantation [60].

With earlier conversion to an everolimus-based regimen (at <6 months post-transplant), renal benefit was demonstrated. For instance, in the CENTRAL study, recipients were randomized at Week 7 post-transplant to either continue s-cyclosporine + MPA-based regimen or switch to everolimus + MPA (overnight cyclosporine withdrawal). The intent-to-treat (ITT) population analysis showed numerically higher renal function in the everolimus versus MPA arm and, in the on-treatment subpopulation, renal benefit was observed for up to 3 years of follow-up, with significantly greater increase in mean measured GFR in the everolimus versus the s-cyclosporine group (an increase of 7.9 mL/min in the everolimus treatment group vs a decrease of 1.4 mL/min in the s-cyclosporine group by Month 36, $p = 0.001$). In addition, no significant difference in the presence of DSA between the everolimus and control arms at Month 36 was observed [63,66].

Consistent with these data, the ZEUS study demonstrated renal benefit with everolimus use for up to 5 years of follow-up when conversion occurred at 4.5 months after kidney transplantation. Patients were randomized to continue s-cyclosporine regimen or switch to everolimus (CNI withdrawal). Significant improvement in renal function with everolimus versus s-cyclosporine was noted at 1 year and this was maintained up to 5 years, thus demonstrating long-term renal benefit of early conversion to everolimus [61,62,71].

In the 24-month ELEVATE study, a larger study than ZEUS or CENTRAL, >700 patients were randomized to receive either everolimus + MPA (CNI withdrawal) or remain on sCNI therapy (tacrolimus or cyclosporine) + MPA at 10–14 weeks post-transplant. No significant difference in the primary endpoint of change in eGFR from switch to everolimus up to Month 12 was observed in everolimus versus CNI groups. However, the observed mean eGFR remained significantly higher in the everolimus group versus the CNI group (with the exception of the Month 12 time point), up to Month 24. In addition, the incidence of de novo DSA was similar in the everolimus versus CNI groups in a subset analysis [64].

Three studies, including CENTRAL and ELEVATE, have investigated the progression of renal interstitial fibrosis (IF) and tubular atrophy (IF/TA), finding no marked differences between everolimus versus CNI groups [63,64,66,72]. In contrast to this, the MECANO study (NTR1615), in which 224 patients were randomized at 6 months post-transplant to receive everolimus-, cyclosporine-, or MPA-based regimens, demonstrated significantly decreased IF and inflammation in the everolimus-based group at Month 24 [73].

In summary, in patients remaining on therapy, treatment with everolimus can maintain clinically significant renal function, and long-term renal benefit can be achieved with early everolimus-facilitated reduction or withdrawal of CNI therapy. Thus, it is crucial to initiate everolimus early rather than late, to preserve renal function. In addition, there is some evidence to suggest that treatment with everolimus may decrease IF/TA progression; however, longer-term confirmatory evidence is required. As noted previously, drug discontinuation rates were generally higher with everolimus-based versus CNI-based regimens,

Table 2

Key clinical studies of everolimus in the context of reduced CNI exposure in liver, heart and lung transplant recipients. Findings of statistical significance highlighted in bold.

Study	Immunosuppressive regimen base	Month (M) of follow-up	Efficacy failure %	Renal function (mL/min/1.73 m ²)
Liver (time of EVR conversion post-transplant); number of patients (n)				
H2304 (30±5 days) n=719 ^a [23, 75, 83]	EVR (C ₀ 3–8 ng/mL) + rTAC	M12 M24 M36	6.7 ^f 10.3 ^f 11.5 ^f	80.9 74.7 78.7
	sTAC-based regimen	M12 M24 M36	9.7 ^f 12.5 ^f 14.6 ^f	70.3 p<0.001 EVR/ rTAC vs sTAC (M12) 67.8 p=0.007 EVR/ rTAC vs sTAC (M24) 63.5 p<0.001 EVR/ rTAC vs sTAC (M36)
H2307 (30±5 days) n=284 [76, 84]	EVR (C ₀ 3–8ng/mL) + rTAC	M12 M24	5.1 ^f 9.0 ^f	81.2 78.4
	sTAC-based regimen	M12 M24	5.8 ^f 8.0 ^f	76.5 75.3
SIMCER (4 weeks) n=188 [81]	EVR (C ₀ 6–10 ng/mL) + MPA + TAC withdrawal (stepwise reduction followed by withdrawal by Month 4)	M6	10.0 ^f	95.8
	sTAC + MPA	M6	4.3 ^f	76.0 p<0.001 EVR/MPA vs sTAC MPA (M6)
PROTECT (4 weeks) n=203 [79, 85]	EVR (C ₀ 5–12 ng/mL) + CNI withdrawal (TAC or CsA reduction for 8 weeks, followed by withdrawal)	M12 M60	20.8 ^g 9.8 ^g	80.3 77.0
	sCNI-based regimen (TAC or CsA)	M12 M60	20.4 ^g 7.5 ^g	72.1 p=0.021 sCNI group minus EVR group (M12) 65.3 p=0.029 EVR vs sCNI (M60)
Heart (time of EVR conversion post-transplant); number of patients (n)				
A2310 (<3 months) n=721 ^a [87]	EVR (C ₀ 3–8 ng/mL) + rCsA	M12 M24	35.1 ^h 39.4 ^h	59.4 59.5
	MMF + sCsA	M12 M24	33.6 ^h 41.3 ^h	64.7 p=0.009 EVR/ rCsA vs MMF/sCsA (M12) 64.5 p=0.020 EVR/ rCsA vs MMF/sCsA (M24)
SCHEDULE (<3 months) n=115 [91, 92]	EVR (C ₀ 6–10 ng/mL) + MMF (CNI withdrawal at 7 weeks after randomization)	M12 M60 ^d	33.0ⁱ 50.0ⁱ	79.8ⁿ 74.7ⁿ
	sCNI +MMF	M12 M60 ^d	11.0ⁱ p<0.001 EVR/MMF vs sCNI/MMF (M12) 23.0ⁱ p<0.01 EVR/MMF vs sCNI/MMF (M60)^d	61.5ⁿ p<0.001 EVR/MMF vs sCNI/MMF (M12) 62.4ⁿ p=0.004 EVR/MMF vs sCNI/MMF (M60)^d
MANDELA (6 months) n=162 [90]	EVR (C ₀ 5–10 ng/mL) + rCsA or rTAC	M18	6.8^h	52.9
	EVR (C ₀ 5–10 ng/mL) + MPA (CNI withdrawal: CNI reduction over 8 weeks, with withdrawal within 3 months)	M18	22.5^h p=0.009	64.1 p<0.001 EVR/rCNI vs EVR/MPA
NOCTET (≥1 year) n=282 ^b Heart and lung transplant recipients [30, 89, 102]	EVR (C ₀ 3–6 ng/mL) + rCNI (CsA or TAC) ^c	M12	4.3 ^j	+4.6 change from baselineⁿ
		M24-60 ^g	1.4 ^k	-1.5 change from baselineⁿ
	sCNI ^c	M12	2.8 ^j	-0.5 change from baselineⁿ p<0.0001 EVR/rCNI vs sCNI at M12
		M24-60 ^g	2.2 ^k	-7.2 change from baselineⁿ (p=0.006 EVR/rCNI vs sCNI at M60)
Lung (time of EVR conversion post-transplant); number of patients (n)				
Snell et al. (3–36 months) (n=213) Lung or heart/ lung transplant recipients [95]	EVR + sCsA	M12 M24	21.8^p 43.6 ^p	Not reported
	AZA + sCsA	M12 M24	33.9^p p=0.046 44.6 ^p	Not reported
Glanville et al. (4–12 weeks) n=164 [96]	EVR (C ₀ 3–8 ng/mL) + rCsA	M36	28.6 ^j	GFR not reported (creatinine = 152 +/- 98 μmol/L)
	MPS + CsA	M36	30.0 ^j	GFR not reported (creatinine = 160 +/-112 μmol/L)
Strueber et al. (28 days) N=190 [97]	EVR (C ₀ 6–8 ng/mL) + rCsA	M24	14.0 ^j	52.0
	MMF + sCsA	M24	21.0 ^j	56.0
4EVERLUNG (3–18 months) N=130 [98]	EVR (C ₀ 3–5 ng/mL) + rCNI (TAC or CsA)	M12	7.0 ^m	64.5
	sCNI regimen (TAC or CsA)	M12	14.0 ^m	54.6 p<0.001 EVR/rCNI vs sCNI

^aIn the H2304 study an EVR + TAC withdrawal treatment arm was also included but randomization to it was prematurely terminated. In the A2310 study an EVR C₀: 6–12 ng/mL + r-cyclosporine treatment arm was also included but was prematurely terminated.

^bIn the NOCTET study: 190 heart and 92 lung transplant recipients; ^cIn the NOCTET study, patients receiving MPA and/or AZA were maintained on these treatments.

^dFollow-up visit between M60–84; ^eLast routine visit was at 5 years post-randomization or later.

Efficacy failure is the endpoint consisting of: ^ftreated BPAR, graft loss, or death; ^gBPAR, graft loss, death, or loss to follow-up; ^hBPAR, acute rejection associated with hemodynamic compromise, graft loss/re-transplant, death, or loss to follow-up; ⁱtreated BPAR (from Weeks 7–11 [M12]; from time of transplantation [M60]); ^jtreated BPAR; ^krejection ^lbronchiolitis obliterans syndrome; ^mnew onset chronic lung allograft dysfunction; ^pDecline in FEV > 15%, graft loss, or death, or lost to follow-up.

Renal function: estimated GFR (using MDRD, Nanvikell, Cockcroft-Gault or CKD-EPI formulas); ⁿmeasured GFR.

AZA, azathioprine; BPAR, biopsy-proven acute rejection; CNI, calcineurin inhibitor; CsA, cyclosporine; C₀, trough level; EVR, everolimus; GFR, glomerular filtration

rate; MDRD, modification of diet in renal disease; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MPS, mycophenolate sodium; rCNI, reduced-exposure CNI; rCsA, reduced-exposure CsA; rTAC, reduced-exposure tacrolimus; sCNI, standard-exposure CNI; sCsA, standard-exposure CsA; sTAC, standard-exposure tacrolimus; TAC, tacrolimus.

potentially due to the different AE profile of everolimus (see Section 4).

3.2. Evidence in liver, heart and lung transplantation

Early CNI reduction is also an important management strategy for maintaining long-term outcomes in non-kidney transplant recipients. This section describes efficacy and renal function outcomes from key clinical studies investigating the use of everolimus to reduce or withdraw CNI exposure across liver, heart, and lung transplant recipients (Table 2).

3.2.1. Anti-rejection efficacy

In liver transplant recipients, the safety, tolerability, and efficacy of everolimus in combination with s-cyclosporine in de novo liver transplant recipients was demonstrated in a Phase II study, paving the way for additional studies in this setting [74]. With tacrolimus-based regimens becoming the standard-of-care, several recent studies have investigated everolimus in combination with r-tacrolimus or tacrolimus withdrawal and found comparable efficacy to standard tacrolimus (s-tacrolimus) for up to 5 years of follow-up [75–82].

In the pivotal H2304 study (NCT00622869), deceased-donor liver transplant recipients were randomized to receive everolimus (C_0 3–8 ng/mL) + r-tacrolimus-based regimen ($n = 245$) versus s-tacrolimus-based regimen ($n = 243$) at 30 ± 5 days post-transplant [23]. Randomization to a third arm, everolimus + tacrolimus withdrawal, was prematurely terminated due to a high acute rejection rate, clustered around the time when tacrolimus was eliminated [23]. Non-inferiority of the primary composite efficacy failure endpoint (treated BPAR, graft loss, or death) was reported across the two treatment arms at 12 months, which was maintained to Month 36, with a significantly lower rate of treated BPAR observed with everolimus + r-tacrolimus [23,75,83].

The similarly designed H2307 study (NCT01888432) – differing to study H2304 in its patient population, with H2307 being the first to investigate everolimus in the setting of living-donor transplants – included 284 living-donor liver transplant recipients [76]. Non-inferiority of the primary composite efficacy failure endpoint (treated BPAR, graft loss, or death) was reported across the two treatment arms at 12 months, which was maintained to Month 24 [76,84]. In addition, a pooled analysis of the H2304 and H2307 studies at 24 months of follow-up demonstrated comparable efficacy between the two treatment arms, and a numerically lower incidence of treated BPAR in the everolimus + r-tacrolimus treatment arm versus s-tacrolimus, thus providing further evidence to support the use of early everolimus-facilitated tacrolimus reduction in living- or deceased-donor liver transplants [77].

Despite the high acute rejection rate observed in the prematurely terminated everolimus-facilitated tacrolimus withdrawal arm in the H2304 study, the feasibility of everolimus-facilitated CNI withdrawal regimens has been demonstrated in further clinical studies [78,79,81,82,85]. In the PROTECT study (NCT00378014), evaluating everolimus + CNI withdrawal versus sCNI, clustering of acute rejections at the time of tacrolimus withdrawal was avoided by a stepwise CNI withdrawal, with comparable anti-rejection efficacy between the two treatment arms at Month 12 which was maintained up to 5 years [78,79,85]. In contrast to the H2304 study, patients in PROTECT underwent a more gradual tacrolimus withdrawal over a maximum of 8 weeks, compared to a maximum of 4 weeks in H2304. Patients in PROTECT also received induction with an IL-2 antibody (unlike in H2304) which may have also contributed to the discrepancy observed in early efficacy outcomes in the two studies [78].

Comparable efficacy of everolimus-facilitated tacrolimus withdrawal regimens has also been observed with gradual tacrolimus withdrawal in the multicenter SIMCER study (NCT01625377) [81]. In this study of 188

de novo liver transplant recipients, everolimus + MPA (with tacrolimus discontinued by Month 4) demonstrated similar rates of treatment failure (treated BPAR, graft loss, or death) at Week 24 compared to a s-tacrolimus + MPA-based regimen. Rates of BPAR were more frequent with everolimus + MPA groups versus s-tacrolimus + MPA, however, the majority of episodes were mild and less frequent than those observed in the H2304 and PROTECT studies [81]. An observational study following patients who completed the 6-month SIMCER study has recently demonstrated that treated BPAR is rare in both groups at 24 months of follow-up [82]. In addition, data from 1045 patients receiving everolimus included in the French multicenter observational Everolimus Liver registry (EVEROLIVER; evaluating efficacy, renal function, and safety of everolimus use in clinical practice) demonstrated that everolimus-facilitated CNI withdrawal (stepwise reduction) was feasible in 50% and 58% of patients at 12 months and 60 months following everolimus introduction, respectively, and that incidence of treated BPAR at Month 60 after conversion to everolimus was similar to that observed at Month 36 in the H2304 study [86].

In heart transplant recipients, studies including A2310 (NCT00300274) and NOCTET (Nordic Certican Trial in HEart and lung Transplantation), have demonstrated comparable efficacy of everolimus + r-cyclosporine-based regimens versus sCNI-based regimens up to 5 years of follow-up [30,87–89], both in de novo patients and in maintenance patients with late introduction of everolimus.

In terms of studies investigating everolimus-facilitated CNI withdrawal in heart transplant recipients, the MANDELA study (NCT00862979) was the first to directly compare two everolimus-facilitated CNI reduction strategies (reduction vs withdrawal) [90]. It demonstrated a significantly higher incidence of treatment failure (mainly driven by BPAR) in the everolimus-CNI withdrawal group (where CNI was decreased over an 8-week period) versus the everolimus + MPA + rCNI group (r-cyclosporine or r-tacrolimus) at 18 months of follow-up. However, no rejection episode led to hemodynamic compromise and, as 40% of BPAR episodes occurred in patients with a low everolimus exposure (<5 ng/mL), the incidence of BPAR in the CNI withdrawal arms could potentially be reduced with more careful regulation of blood concentrations [90].

Following conversion to CNI-free treatment in the SCHEDULE study (NCT01266148), which investigated everolimus + MMF + CNI withdrawal (withdrawn at Weeks 7–11 post-transplant) versus MMF + sCNI, both the incidence of BPAR overall and the incidence of treated rejection were significantly higher in the everolimus group, although no episodes of hemodynamic compromise were noted [91,92].

In addition to graft rejection, cardiac allograft vasculopathy (CAV) is a major concern in heart transplant recipients for long-term outcomes. In studies enrolling de novo recipients, reduced CAV has been observed for up to 12 months with everolimus-facilitated CNI-reduction [22,87] and up to 7 years for CNI-withdrawal [92]. On the other hand, late conversion to everolimus-based regimens failed to show effects on CAV progression [93] and everolimus did not appear to influence late CAV progression in an observational study [94].

In lung transplant recipients, the possible advantages of everolimus use were highlighted in an early multicenter randomized study led by Snell et al. investigating everolimus versus azathioprine, each as part of a s-cyclosporine-based regimen, with the everolimus treatment arm demonstrating a significant slowing of loss of lung function [95]. Further randomized studies investigating everolimus-facilitated CNI reduction have demonstrated comparable, and in some cases improved, efficacy versus sCNI-based regimens with up to 3 years of follow-up [96–98].

In a multicenter randomized study in lung transplant recipients, led by Glanville et al. (EudraCT No.2004-01290-25), investigating everolimus + rCNI versus mycophenolate sodium (MPS) + sCNI initiated

early post-transplant, comparable efficacy between treatment arms was observed for incidence of bronchiolitis obliterans syndrome (BOS; the most common manifestation of chronic allograft dysfunction) at 3 years of follow-up [96]. In addition, a significantly lower rate of acute rejection was observed with everolimus + rCNI versus MPS + sCNI [96]. Similarly, a single-center, randomized study led by Strueber et al. (NCT00402532) showed that 2-year BOS-free survival was comparable between everolimus + r-cyclosporine versus mycophenolate mofetil (MMF) + s-cyclosporine treatment arms (ITT population), with significant difference in favor of the everolimus treatment arm in the per protocol population [97]. Episodes of BPAR were also lower in the everolimus + r-cyclosporine arm versus the MMF + s-cyclosporine treatment arm, demonstrating that lowering of cyclosporine levels in the everolimus arm did not lead to a higher rate of acute rejection [97]. Finally, the multicenter, randomized 4EVERLUNG study (NCT01404325) showed comparable efficacy of an everolimus + rCNI-based regimen versus an sCNI-based regimen over 12 months of follow-up in patients with impaired renal function, with rates of chronic lung allograft dysfunction, BPAR, and death being similar between groups [98].

Overall, everolimus-based CNI reduction regimens, initiated as early as <3 months post-transplant, have shown anti-rejection efficacy across liver, heart, and lung comparable to sCNI regimens. Despite higher BPAR rates observed with CNI withdrawal versus sCNI regimens in some studies, a stepwise conversion approach has been shown to facilitate optimal immunosuppression and help to avoid acute rejection episodes at the time of conversion. In addition, a retrospective case control analysis across heart, lung, kidney, and liver transplant recipients has reported a similar incidence of de novo DSA at 12 months of follow-up in patients converted to everolimus + rCNI from cyclosporine- or tacrolimus-based regimens after 6 years of transplantation [99].

3.2.2. Renal function

As in kidney transplantation, the potential for everolimus-facilitated CNI reduction to preserve long-term renal function has been investigated in numerous studies across liver, heart, and lung transplant recipients.

In liver transplant recipients, several clinical studies, including H2304, H2307, and PROTECT have demonstrated preserved, and in some cases improved, renal function with everolimus-based CNI reduction regimens for up to 5 years of follow-up [23,75–77,79,80,83]. In the H2304 study, superior renal function was maintained for up to 3 years post-transplant in deceased-donor liver transplant recipients receiving everolimus + r-tacrolimus versus s-tacrolimus [23,75,83]. Furthermore, a pooled analysis of the H2304 and H2307 studies, demonstrated significantly better renal function in everolimus + r-tacrolimus versus s-tacrolimus arm at 24 months of follow-up, particularly in patients with normal/mildly decreased renal function (chronic kidney disease stage 1/2) at randomization [77].

In terms of everolimus-facilitated CNI withdrawal in liver transplant recipients, the PROTECT study demonstrated improved renal function with an everolimus-based CNI-free regimen versus continued CNI for up to 5 years of follow-up [78,79]. In the SIMCER study, the primary endpoint of change in eGFR from randomization to Month 6 was superior with everolimus + MPA (and tacrolimus withdrawal) versus s-tacrolimus + MPA, demonstrating a significant renal benefit with everolimus-facilitated tacrolimus withdrawal and MPA [81]. This benefit was maintained for a further 12 months in an observational study following 143 patients who completed the SIMCER study, with a trend to higher mean eGFR from Months 12 to 24 [82].

Renal benefit with everolimus has also been observed in the EVEROLIVER registry, which has reported an improvement in mean eGFR in patients with baseline eGFR < 60 mL/min/1.73 m² up to Month 60 and maintenance of mean eGFR in patients with baseline eGFR ≥ 60 mL/min/1.73 m² up to Month 36 post-everolimus conversion [86]. Interestingly, among patients with baseline eGFR < 60 mL/min/1.73 m²,

55% of those who were converted to everolimus within 3 months post-transplant (early conversion) and 39.4% of those converted between 4 and 12 months post-transplant (mid-term conversion) experienced an improvement in renal function at Month 36 versus only 20.9% of patients who were converted to everolimus beyond 12 months (late conversion), demonstrating an association between early conversion to an everolimus-based regimen and an improvement in renal function [86].

In heart transplant recipients, an early randomized study investigating everolimus + r-cyclosporine versus MMF + r-cyclosporine in 34 mid-term heart transplant recipients with a baseline creatinine clearance of 43.5 ± 9.1 mL/min highlighted renal function preservation in both treatment arms at 12 months [100]. Follow-up to 3 years showed that renal function remained stable with everolimus and a significant improvement in renal function was demonstrated in patients without proteinuria at baseline, suggesting that the absence of baseline proteinuria can identify patients who may obtain improved renal function by conversion to an everolimus-based strategy [101]. Further studies have demonstrated comparable, and in some cases improved, renal function with everolimus-based CNI reduction regimens for up to 5 years of follow-up [30,87–90,92]. In study A2310, comparable renal function of everolimus (C₀ 3–8 ng/mL) + r-cyclosporine versus MMF + cyclosporine groups at Month 24 was observed only when the predefined levels of cyclosporine trough concentration were achieved. Higher than target cyclosporine levels are likely to have masked any renal benefit with everolimus [87]. In the NOCTET study investigating everolimus (C₀ 3–6 ng/mL) + rCNI versus sCNI-based therapy in maintenance heart and lung transplant recipients with renal impairment, significantly improved renal function at Month 12 was observed in the everolimus + rCNI arm. Patients with a shorter time to everolimus conversion post-transplant experienced the greatest improvement [30,102]. In the everolimus treatment arm, renal function remained stable to the last study visit (at 5 years or later, with 125 heart transplant recipients and 38 lung transplant recipients comprising the ITT population) versus a decrease in the s-cyclosporine treatment arm, therefore demonstrating better long-term preservation of renal function with everolimus [89].

Renal benefit with everolimus has also been observed with everolimus-facilitated CNI withdrawal regimens in heart transplant recipients [90,92,103]. In the MANDELA study, the everolimus + CNI withdrawal group demonstrated superior renal function versus the everolimus + rCNI group at 18 months of follow-up [90]. Similarly, the SCHEDULE study demonstrated renal benefit with a significantly higher measured GFR at 12 months post-transplant (primary efficacy endpoint) attained with an everolimus-cyclosporine withdrawal regimen versus a s-cyclosporine-based regimen [91]. This benefit was maintained for a follow-up of 5–7 years post-transplant [92].

In lung transplant recipients, at least comparable renal function with everolimus-based CNI reduction regimens has been demonstrated in clinical studies [96–98]. In the multicenter, randomized study led by Glanville et al., the development of renal dysfunction (as indicated by creatinine levels) was comparable between the everolimus + r-cyclosporine group versus the MPS + s-cyclosporine group at 3 years of follow-up [96]. Similarly, in the single-center, randomized study led by Strueber et al., overall comparable renal function was observed between the two treatment arms (everolimus + r-cyclosporine vs MMF + s-cyclosporine) for up to 2 years of follow-up, however there was a significant decrease in kidney function observed in both groups within the first 6 months that stabilized at 1 year [97]. In contrast to these findings, the 4EVERLUNG study demonstrated significantly better renal function in the everolimus + rCNI group versus sCNI group over 12 months of follow-up, with mean eGFR increasing in the everolimus group in the first week after randomization, becoming significantly higher than the sCNI group after Month 1, and remaining so thereafter [98].

Overall, renal function was maintained or improved among patients treated with everolimus-based regimens across solid organ transplantation. Some studies showed improvement in eGFR among renal-impaired patients. Introduction of everolimus in de novo or

Table 3

AEs and safety findings of interest in key studies of EVR across organ transplant indications.

Study	Study groups	Drug discontinuations	AE and safety findings (%)							
			SAEs	Hyperlipidemia	Proteinuria	Malignancy	CMV	BKV	Wound healing events	Stomatitis
Kidney (time of EVR conversion post-transplant); month of follow-up (M)										
A2309 (≤24 h) M24 [70]	EVR (C ₀ 3–8 ng/mL) + rCsA	28.5	64.2	20.4	11.3	3.3	1.5	0.7	2.2	6.9
	EVR (C ₀ 6–12 ng/mL) + rCsA	30.6	69.4	22.3	13.7	2.5	0.4	1.4	4.3	8.3
	MPA + sCsA	20.5	61.5	16.1	8.1	4.8	6.2	4.8	1.5	3.3
A1202 (≤24 h) M12 [49]	EVR (C ₀ 3–8 ng/mL) + rCsA	4.9	44.3	45.9	13.1	3.3	4.9	na	39.3	23.0
	MMF + sCsA	1.6	54.1	31.1	8.2	0.0	34.4	na	11.5	16.4
CERTES/LATAM (≤24 h) M12 [50]	EVR (C ₀ 3–12 ng/mL) + CsA (withdrawal by M4–6)	9.1	29.1	7.3 Dyslipidemia	7.3	na	na	na	7.2	na
	EVR (C ₀ 3–12 ng/mL) + rCsA	10.2	23.7	3.4 Dyslipidemia	1.7	na	na	na	3.4	na
TRANSFORM (≤24 h) M24 [58]	EVR (C ₀ 3–8 ng/mL) + rCNI (CsA or TAC)	27.2	na	13.4	14.1	7.2	2.8	5.8	19.8 ^a	3.0
	MPA + sCNI (CsA or TAC)	15.0	na	7.4	7.0	9.0	13.5	10.3	16.2 ^a	0.6
ATHENA (≤24 h) M12 [56]	EVR (C ₀ 3–8 ng/mL) + TAC	31.0	76.7	na	na	na	6.2	17.6	30.5	na
	EVR (C ₀ 3–8 ng/mL) + CsA	34.8	72.7	na	na	na	2.5	9.1	28.3	na
	MPA +TAC	16.2	66.2	na	na	na	20.6	22.5	33.3	na
ASCERTAIN (>6 months) M24 [60]	sCNI-based regimen (TAC or CsA)	4.1	42.3	8.9	8.9	5.7	na	na	na	2.4
	EVR (C ₀ 8–12 ng/mL) + CNI withdrawal (withdrawal when EVR C ₀ reached)	28.3	56.7	28.3	16.5	7.1	na	na	na	29.1
	EVR (C ₀ 3–8 ng/mL) + rCNI	16.7	54.2	23.6	13.2	7.6	na	na	na	11.8
CENTRAL (7 weeks) M12 [66]	sCsA + MPA	3.0	38.0	9.0	0.0	2.0	13.0	1.0	na	1.0
	EVR (C ₀ 6–10 ng/mL) + MPA (CsA withdrawal; overnight withdrawal)	25.5	53.9	12.7	4.9	2.0	8.8	2.0	na	12.7
ZEUS (4.5 months) M12-60 [61, 62]	EVR (C ₀ 6–10 ng/mL) + MPA (CsA withdrawal) stepwise withdrawal over a maximum of 4 weeks)	0.6	17.4	na	na	na	2.6	na	na	na
	sCsA + MPA	0.7	11.7	na	na	na	3.4	na	na	na
ELEVATE (10–14 weeks) M24 [64]	EVR (C ₀ 6–10 ng/mL) + MPA (CNI withdrawal; overnight or stepwise over 1 week)	23.6	54.8	na	15.3	na	4.0	1.4	0.9	6.8
	sCNI therapy (TAC or CsA) + MPA	8.4	49.0	na	3.6	na	6.1	5.0	0.0	0.8
Liver (time of EVR conversion post-transplant); month of follow-up (M)										
H2304 (30±5 days) M36 [23]	EVR (C ₀ 3–8 ng/mL) + rTAC	na	59.4	15.1	0.0	0.9 ^b	2.8	na	11.0 ^a	8.5
	sTAC-based regimen	na	60.0	6.4	0.0	0.8 ^b HCC recurrence	1.6	na	7.9 ^a	1.6
H2307 (30±5 days) M12 [76]	EVR (C ₀ 3–8 ng/mL) + rTAC	12.7	49.3	13.4	na	0 HCC recurrence	4.2	na	7.7	9.9
	sTAC-based regimen	10.6	43.3	3.5	na	8.1 HCC recurrence	5.7	na	5.0	3.5
SIMCER (4 weeks) M6 [81]	EVR (C ₀ 6–10 ng/mL) + MPA + TAC withdrawal (stepwise reduction followed by withdrawal by month 4)	17.8	46.7	7.8 Dyslipidemia	na	0.0 HCC recurrence	5.6	na	na	na
	sTAC + MPA	3.2	29.8	1.1 Dyslipidemia	na	0.0 HCC recurrence	5.3	na	na	na
PROTECT (4 weeks) M60 [79]	EVR (C ₀ 5–12 ng/mL) + CNI withdrawal (TAC or CsA reduction for 8 weeks, followed by withdrawal)	17.1	63.4	na	9.8	4.9 HCC recurrence	na	na	na	na
	sCNI-based regimen (TAC or CsA)	12.5	70.0	na	0	5.0 HCC recurrence	na	na	na	na
Heart (time of EVR conversion post-transplant); month of follow-up (M)										
A2310 (<3 months) M24 [87]	EVR (C ₀ 3–8 ng/mL) + rCsA	33.3	74.9	37.3	3.2	8.2	7.2	na	24.4 Sternal	9.7
	sCNI +MMF	25.7	62.7	26.9	1.5	7.8	21.6	na	18.7 Sternal	6.0
SCHEDULE (<3 months) M12 [103]	EVR (C ₀ 6–10 ng/mL) + MMF (CNI withdrawal at 7 weeks after randomization)	na	47.1	na	na	na	5.9	na	38.0 ^c	na
	sCNI +MMF	na	45.1	na	na	na	31.4	na	22.0 ^c	na
MANDELA (6 months) M18 [90]	EVR (C ₀ 5–10 ng/mL) + rCsA or rTAC	15.5	47.6	10.7	na	na	13.1	na	na	na
	EVR (C ₀ 5–10 ng/mL) + MPA (CNI withdrawal: CNI reduction over 8 weeks, with withdrawal within 3 months)	17.9	37.2	6.4	na	na	6.4	na	na	na
NOCTET ^d (≥1 year) M12 [30, 89, 102]	EVR (C ₀ 3–6 ng/mL) + rCNI (CsA or TAC) ^e	na	46.8	na	na	na	na	na	na	na
	sCNI ^e	na	31.0	na	na	na	na	na	na	na
Lung (time of EVR conversion post-transplant); month of follow-up (M)										
Snell et al. ^d (3–36 months) M12 [95]	EVR + sCsA	na	63.1	19.8	na	7.2	7.2	na	na	na
	AZA + sCsA	na	43.1	4.5	na	4.5	10.8	na	na	na
Glanville et al. (4–12 weeks) M36 [96]	EVR (C ₀ 3–8 ng/mL) + rCsA	54.8	82.0	32.0	na	na	4.0	na	na	7.0
	MPS + CsA	42.0	79.0	24.0	na	na	12.0	na	na	1.0
Strueber et al. (28 days) M24 [97]	EVR (C ₀ 6–8 ng/mL) + rCsA	55.0	57.0	na	na	na	0.0	na	na	na
	MMF + sCsA	43.0	42.0	na	na	na	2.0	na	na	na
4EVERLUNG (3–18 months) M12 [98]	EVR (C ₀ 3–5 ng/mL) + rCNI (TAC or CsA)	25.0	43.0	na	0.0	na	15.0	0.0	na	na
	sCNI regimen (TAC or CsA)	0.0	35.0	na	1.6	na	22.0	1.6	na	na

Definitions and criteria of these selected events vary between studies.

^aIncidence at 12 months; ^bHCC recurrence at Month 24–36; ^cWound complications as reported in a post-hoc analysis of SCHEDULE (Rashidi et al. 2016 [142]);

^dIncluded both heart and lung transplant recipients; ^eIn the NOCTET study, patients receiving MPA and/or AZA were maintained on these treatments.

AE, adverse event; AZA, azathioprine; BKV, BK virus; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CsA, cyclosporine; C₀, trough level; EVR, everolimus; HCC, hepatocellular carcinoma; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MPS, mycophenolate sodium; na, not available; rCNI, reduced-exposure CNI; rCsA, reduced-exposure CsA; rTAC, reduced-exposure TAC; sCNI, standard-exposure CNI; sCsA, standard-exposure CsA; sTAC, standard-exposure tacrolimus; SAE, serious adverse event; TAC, tacrolimus.

maintenance regimens as part of a CNI reduction or withdrawal strategy can potentially reduce the risk of end-stage renal disease in the long term. Adherence to both CNI and everolimus target trough concentrations are key for preserving renal function in the long term.

4. Tolerability and AEs of everolimus-based regimen in adult solid organ transplantation

Generally, everolimus is well tolerated in patients receiving a transplant. However, like most immunosuppressive agents, everolimus is associated with potential AEs. This section summarizes the tolerability and AEs of interest reported in key clinical studies investigating the use of everolimus-based CNI reduction regimens across solid organ transplant indications, with a focus on those that are associated with the mTOR inhibitor class of immunosuppressant agents (Table 3). In most studies, drug discontinuation rates were higher with everolimus-based versus CNI-based regimens.

4.1. Viral infections

Cytomegalovirus (CMV) infections are a frequent complication in transplant recipients and can result in graft injury [104,105]. Several studies have reported that the incidence of CMV was lower with everolimus versus CNI-based comparator treatment arms across solid organ transplant indications [58,90,97,106–108]. In the TRANSFORM and ATHENA studies in kidney transplant recipients, the incidence of CMV infection was lower with everolimus-facilitated CNI reduction versus sCNI [56,58]. Of interest, a recent post-hoc analysis including 90 patients completing 12 months of treatment in the ATHENA study revealed that everolimus-treated patients retained CMV-specific T-cell functionality, which may contribute to enhanced protection against CMV infections [109]. Contrary to these observations, in the H2304 and H2307 studies in liver transplant recipients, there was no statistically significant difference observed between CMV infections in the everolimus + r-tacrolimus group versus the s-tacrolimus group. However, everolimus was not administered until Day 30, so this late introduction may have resulted in the statistically non-significant difference between groups [23,76].

BK virus (BKV) commonly affects kidney transplant recipients because of its latency in the kidney and can result in loss of graft function [110,111]. Evidence for the benefit of everolimus-based regimens in reducing the risk of BKV infection is limited in prospective studies, however BKV infections were found to be significantly less frequent with everolimus versus MPA in the TRANSFORM and ATHENA studies [56,58,108]. Additionally, a small study in kidney transplantation has also reported everolimus-associated reduction in BKV replication versus the CNI group [112]. While rare, BKV infection can occur in non-renal transplant recipients after anti-rejection therapy or with renal dysfunction in patients with CMV infection or hypogammaglobulinemia [113].

4.2. Hyperlipidemia

Hyperlipidemia is a known side effect of many immunosuppressive agents, including everolimus [114–116]. Studies have reported higher levels of hyperlipidemia with everolimus versus control [58,75]. Lipid levels usually peak 2–3 months after transplantation, stabilizing or decreasing thereafter, a finding that may be related to increased use of

lipid-lowering agents [116]. In the H2304 study, lipid parameters stabilized after Month 12, although a higher proportion of patients received lipid-lowering agents in the everolimus + r-tacrolimus versus s-tacrolimus group [23].

4.3. Cardiovascular events

Despite higher lipid levels observed in some studies, major cardiovascular events are similar, and in some cases lower, with everolimus treatment versus control across solid organ transplant indications [108,117–119]. In a post hoc analysis of the H2304 study in liver transplant recipients, the risk of major cardiac events was found to increase with deteriorating renal function post-transplantation and everolimus-based immunosuppression improved both renal function and the risk of major cardiac events versus standard tacrolimus therapy [120]. In kidney transplant recipients, a randomized controlled study comparing the cardiovascular profile of everolimus with tacrolimus indicated a reduction of concentric left ventricular hypertrophy following everolimus conversion [118].

4.4. Proteinuria

An increase in proteinuria level has been noted with de novo use of everolimus; however, nephrotic proteinuria is rare [23,27]. In some patients, the increase in proteinuria observed in transplant patients is explained by mTOR inhibitor-induced podocyte damage, which appears to be driven by differential mTOR regulation during therapy with mTOR inhibitors and the downstream effects of this on molecular pathways in podocytes [121].

Proteinuria related to mTOR inhibitors appears to be dose-dependent. In a descriptive analysis of data from the A2309 study in de novo kidney transplant recipients, an everolimus C₀ 3–8 ng/mL was associated with the lowest incidence of proteinuria, with proteinuria being more frequent in patients who were either underexposed (<3 ng/mL) or over exposed (>12 ng/mL) to everolimus [122].

In an early randomized study investigating everolimus + r-cyclosporine (C₀ 50–90 ng/mL) versus MMF + r-cyclosporine (C₀ 100–150 ng/mL) in maintenance heart transplant recipients, the occurrence of proteinuria at baseline seemed to influence the subsequent deterioration of renal function in the everolimus group [101]. A significant improvement in renal function with everolimus was only observed in patients without proteinuria at baseline, suggesting that proteinuria levels can be used to stratify patients who may obtain improved renal function by conversion to an everolimus-based therapy [101].

4.5. Malignancy

The risk of developing malignancy is higher among transplant recipients compared to the general population [123–125]. Chronic immunosuppression, increasing age of the recipient, and a history of malignancy are major risk factors for the transplant population [126–129]. Skin cancers and lymphomas are among the most common malignancies [126,127,130,131]. As hepatocellular carcinoma (HCC) is a major reason for liver transplantation, there is also a high risk of post-transplant HCC recurrence [132,133].

Administration of mTOR inhibitor-based immunosuppressive regimens has been shown to be associated with a lower risk for developing

both cutaneous and non-cutaneous malignancies in kidney and heart transplant recipients [134,135]. A recent meta-analysis of randomized renal transplant studies demonstrated a significant reduction in the incidence of malignancy with the use of mTOR inhibitors [136]. Studies with mTOR inhibitor + CNI, showed a significantly reduced risk for tumor incidence versus CNI therapy with a relative risk value of 0.58 [136]. Given the essential role of mTOR in the regulation of cell-cycle progression and proliferation signaling pathways, it is thought that mTOR inhibition may be able to simultaneously reduce the risk of cancer while promoting immunosuppression to protect against allograft rejection [12,134,135]. Everolimus has shown efficacy in preventing various types of malignancy, including HCC [75–77] and skin tumors [134,137,138].

4.6. Wound healing

Wound healing complications have been observed with everolimus use in kidney transplant recipients [116]. A higher incidence of wound healing events was observed in both the A2309 and TRANSFORM studies with everolimus versus control treatment arms [27,108]. Conversely, in the ATHENA study, rates of wound healing complications were comparable between treatment groups [56]. A recent randomized study investigating the risk of wound healing complications and the early use of everolimus after kidney transplantation demonstrated little difference in the incidences of wound complications between immediate or delayed initiation of everolimus post-transplantation [139].

In heart transplant recipients, sternal wound complications, including wound infections, are a key concern post-transplantation and are associated with high morbidity and mortality [140]. Several heart transplant studies have shown numerically higher incidence of wound healing events with everolimus versus control arms, although many of these studies reported no difference in requirement for surgical interventions across treatment groups [87,141,142]. In a randomized study of immediate versus delayed everolimus initiation in heart transplant recipients, no difference in wound healing delays between the two treatment arms was observed, however, delayed introduction of everolimus was found to reduce occurrence of severe pericardial effusion and the need for pericardial drainage [143].

In the liver H2304 study, wound healing events were low and similar across everolimus and control treatment groups, possibly as a consequence of delayed everolimus introduction (everolimus was introduced 1 month after the transplantation procedure to allow for initial wound healing) [23].

4.7. Stomatitis

A number of studies have shown that the incidence of stomatitis is higher with everolimus versus controls across organ transplant indications [58,70,75,87].

In the TRANSFORM study, treatment with an everolimus-based regimen was associated with a significantly higher risk for developing stomatitis/mouth ulcerations, with an incidence of 7.7% versus 2.1% in the everolimus versus MPA treatment arms, respectively, at 12 months of follow-up [108].

4.8. Thrombotic events

Everolimus and CNIs have been associated with thrombotic events and the combination of everolimus with a CNI may increase the risk [116,144]. Thrombotic events are characterized by endothelial cell lesions, leading to intimal cell proliferation, intraluminal narrowing, and thrombi. CNI-induced endothelial cell lesions may be worsened by reduced mTOR inhibitor-induced vascular endothelial growth factor secretion leading to reduction in endothelial cell regeneration and proliferation capability [144].

Thrombotic events have been observed in some studies with

everolimus-based CNI reduction regimens across organ indications [96,97,116,145]. On the other hand, there have also been a number of studies in transplantation with everolimus that have not reported thrombotic events [144]. A prospective study to establish the precise risk of thrombotic events in this setting is needed [145].

4.9. Pulmonary toxicity

Pulmonary toxicity is a class-related effect of mTOR inhibitors and cases of interstitial lung disease/non-infections pneumonitis have been reported with everolimus, although reports are uncommon [44,146,147]. Symptoms are usually mild to moderate and resolve after discontinuation of the drug, although in rare cases it can progress to a severe and potentially fatal event [146].

A pooled analysis of three clinical studies of everolimus in kidney (A2309), heart (A2310), and liver (H2304) transplant recipients found six cases of interstitial lung disease (ILD) in 1437 patients, representing an incidence of 0.4% [148]. In contrast, a retrospective sub-analysis of a clinical study in 102 kidney transplant recipients reported an incidence of everolimus-induced pneumonitis of 12.7% [149]. This high incidence could be partly explained by a higher than recommended trough level of everolimus or a higher incidence of underlying pulmonary disease at baseline in those patients who developed pneumonitis versus those who did not [148].

5. Clinical implications of everolimus in solid organ transplantation

There is robust evidence to support the early use of everolimus in CNI reduction regimens as an alternative to standard CNI regimens across kidney, liver, heart, and lung transplantation to achieve good anti-rejection efficacy and potentially reduce the risks associated with long-term CNI exposure.

The risk of side effects and possible benefits associated with the known safety profile of everolimus should also be assessed as part of an individualized approach for the management of organ transplant recipients [101,150]. The possible benefits and limitations of everolimus are summarized in Fig. 1.

In kidney transplant recipients, everolimus use appears to be appropriate for the treatment of acute rejection in combination with rCNI and low-dose corticosteroids in most low to moderate immunological risk adult patients [150]. Current treatment guidelines generally consider mTOR inhibitors as a second-line treatment, however, considering the anti-viral effects associated with everolimus-based regimens, their wider use could be of benefit to kidney transplant recipients [150]. The results from the ATHENA study favor the use of tacrolimus over cyclosporine as the combination CNI with everolimus, where the aim was to maintain tacrolimus exposure at 3 to 7 ng/mL (as per findings from the landmark ELITE-Symphony study) [56,150,151].

In liver transplant recipients, the early use of everolimus (at 1 month post-transplant) in combination with r-tacrolimus is recommended due to the beneficial effect on renal function, particularly in patients with eGFR <60 mL/min per 1.73 m² [114]. There may also be additional benefits from everolimus treatment due to its anti-proliferative and anti-fibrotic activities, with studies of everolimus demonstrating encouraging results in terms of prevention of HCC recurrence [77], and reduced progression of liver fibrosis in liver transplant recipients with recurrent hepatitis C virus [152].

Based on evidence from heart transplantation studies, early use of everolimus as part of a CNI reduction or withdrawal strategy appears to be appropriate for the maintenance of immunosuppression and protection of renal function [30,90,92,103]. In addition, Everolimus-associated CAV benefit [22,87,92] and reduction of CMV infections [87,103] are also considerations for its use.

In terms of lung transplantation, everolimus-based CNI reduction regimens also appear to be appropriate for maintenance of

immunosuppression and protection of renal function with potential benefit of reduced risk of CMV infection [96–98]. Everolimus-based CNI reduction regimens can therefore be considered in lung transplant recipients with mild-moderate renal dysfunction [98].

6. Conclusion

Everolimus has been widely investigated in large randomized clinical studies that have shown it to have anti-rejection efficacy comparable with standard-of-care regimens across organ transplant indications. Treatment with everolimus can maintain clinically significant renal function, and long-term renal benefit can be achieved with early everolimus-facilitated reduction or withdrawal of CNI therapy (although higher rates of rejection have been observed with CNI withdrawal in some studies). Thus, it is crucial to initiate everolimus early rather than late, to preserve renal function. Adherence to both CNI and everolimus target trough concentrations are key for preserving renal function in the long term and therapeutic drug monitoring is required to optimize the efficacy of everolimus and reduce AEs.

Everolimus provides an alternative to the current standard-of-care in de novo and maintenance solid organ transplantation recipients who are receiving transplantation due to end-stage disease or who have renal insufficiency at the time of transplantation. Moreover, the additional benefits of everolimus in terms of its class, including anti-proliferative and anti-viral effects, suggest it could be a preferred option when considered as part of an individualized approach for the management of organ transplant recipients.

Authors' contributions

All authors contributed to the review and are responsible for the article content.

Funding

Medical writing support/editorial support was funded by Novartis Pharma AG, Basel, Switzerland in accordance with Good Publication Practice (GPP3) guidelines (<http://www.ismmp.org/gpp3>).

Availability of data and material, Code availability, Ethics approval, Consent to participate, Consent for publication

Not applicable.

Declaration of Competing Interest

The authors have the following to disclose: Helio Tedesco-Silva, received research grants and honoraria for consultation and educational activities from Novartis and Pfizer; Faouzi Saliba has received speaker's honoraria and/or research grants from Novartis, Astellas, Chiesi, Gilead, Abbvie, Merck Sharp & Dohme, Pfizer and Baxter; Markus J Barten, received honoraria; Paolo DeSimone, speaker fees from Novartis; Luciano Potena, speakers fee from Abbott and Sandoz; consultancy fees from Novartis and Biotech; Jens Gottlieb, 2018–2021: Breath Therapeutics (Research Grant), Theravance (Advisory), Merck (Advisory), Altara (Advisory), Novartis (Research Grant) Novartis (Speaker's bureau); Apurva Gawai, is an employee of Novartis; Peter Bernhardt, is an employee of Novartis; Julio Pascual, received honoraries from Novartis and Chiesi as speaker and scientific advisor.

Acknowledgments

Aparajita Mandal, PhD and Aruna Meka, PhD, Novartis Healthcare Private Limited, Hyderabad and Nicola Harris, Novartis Pharmaceuticals UK Limited provided medical writing support/editorial support,

which was funded by Novartis Pharma AG, Basel, Switzerland in accordance with Good Publication Practice (GPP3) guidelines (<http://www.ismmp.org/gpp3>).

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