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Everolimus

Therese M. Chapman and *Caroline M. Perry*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Everolimus is an immunosuppressant that blocks growth factor-mediated proliferation of haematopoietic and nonhaematopoietic cells.

▲ Oral everolimus 0.75 or 1.5mg twice daily significantly reduced the incidence of the primary composite endpoint, efficacy failure 6 months after transplantation, compared with azathioprine 1–3 mg/kg/day, in adult cardiac transplant recipients. All patients also received baseline immunosuppression with ciclosporin and corticosteroids.

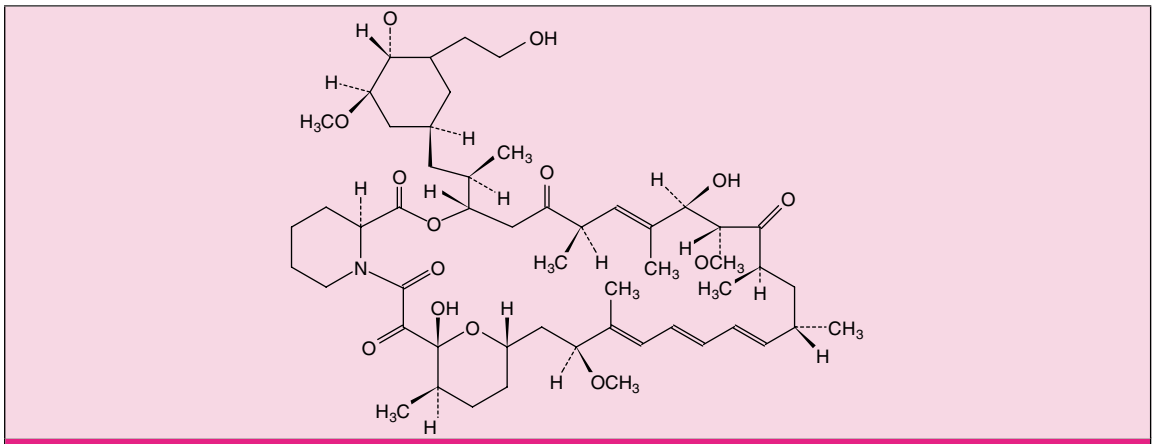
▲ The incidence of efficacy failure remained significantly lower in everolimus recipients than in those receiving azathioprine 1 and 2 years after cardiac transplantation. However, graft and patient survival rates at 1 year were similar in patients receiving everolimus or azathioprine.

▲ The incidence of graft vasculopathy 2 years after transplantation was significantly lower in cardiac transplant recipients receiving everolimus 0.75mg twice daily than in those receiving azathioprine.

▲ The combined incidence of biopsy-confirmed acute rejection, graft loss, death, or loss to follow-up was similar in adult patients receiving everolimus 1.5 or 3 mg/day or mycophenolate mofetil (MMF) 2 g/day 1 or 3 years after renal transplantation. Patients also received baseline immunosupression with ciclosporin and corticosteroids.

▲ Compared with azathioprine and MMF, everolimus is associated with a lower incidence of cytomegalovirus infection in cardiac and renal transplant recipients. Everolimus has been associated with thrombocytopenia, leucopenia and elevated serum lipids and creatinine.

Features and properties of everolimus (Certican™)	
Indication	
Renal and cardiac transplantation	
Mechanism of action	
Immunosuppressant	Proliferation signal inhibitor
Dosage and administration	
Recommended initial dosage	0.75mg twice daily
Route of administration	Oral
Mean pharmacokinetic profile of everolimus over 6 months (oral everolimus 0.75 or 1.5mg twice daily in adult renal transplant recipients)	
Minimum blood concentration	4.3 or 7.2 ng/mL
Median time to peak concentration (at 6 months)	1h
Area under the concentration-time curve (at 6 months)	76 or 138 ng • h/mL
Adverse events	
Most common reasons for premature discontinuation of study drug due to adverse events in cardiac transplant recipients	Renal disorders, infections, leucopenia, gastrointestinal disorders, neurological disorders, anaemia and thrombocytopenia



Everolimus (Certican™)[1] is an orally active 40-*O*-(2-hydroxyethyl) derivative of rapamycin,[1] a macrolide antibiotic produced by *Streptomyces hygroscopicus*. Everolimus, a new oral immunosuppressant, targets the leading causes of late graft loss or chronic allograft dysfunction.[2]

This profile focuses on pharmacological and clinical data relevant to the use of everolimus in renal and cardiac transplant recipients.

1. Pharmacodynamic Profile

Mechanism of Action

• Everolimus, like rapamycin, is a proliferation signal inhibitor that exerts its immunosuppressive effect by blocking interleukin (IL)-2- and IL-15-driven proliferation of haematopoietic (T cells and B cells) and nonhaematopoietic (vascular smooth muscle cells; VSMC) cells by inhibiting the activation of p70 S6 kinase.[2,3] Inhibition of p70 S6 kinase arrests the cell cycle at the G_1 phase preventing progression of the cells to the S phase.[2]

• The inhibitory effect of everolimus is mediated by its forming a complex with the immunophylin FK506 (tacrolimus)-binding protein 12 (FKBP12), which also binds rapamycin.[4] The 50% inhibitory concentration (IC_{50}) for everolimus inhibition of FK506 binding to FKBP12 is 1.8–2.6 nmol/L and is about 3-fold higher than that of rapamycin (0.4–0.9 nmol/L).[3] An x-ray crystal structure of the everolimus/FKBP12 complex revealed a three-dimensional structure for bound everolimus similar to that of rapamycin.[1]

• *In vitro*, everolimus inhibited IL-6–induced proliferation of an IL-6–dependent hybridoma clone (B13-29-15) at concentrations about 2 to 3 times higher than those for rapamycin; IC_{50} values were 0.2–1.4 nmol/L and 0.07–0.5 nmol/L, respectively ($p < 0.01$).[3] However, inhibition of fetal calf serum-stimulated proliferation of VSMC was similar for the two agents (0.9–3.6 versus 0.4–3.5 nmol/L).[3]

• Everolimus significantly inhibited IL-10 synthesis stimulated by anti-CD3mAb (IC_{50}: 13 nmol/L) or LPS (IC_{50}: 36 nmol/L) [p-values not reported] *in vitro*.[5] Furthermore, multiple doses of everolimus (0.75–10mg; frequency of administration not stated) in combination with ciclosporin and corticosteroids significantly inhibited anti-CD3mAb- and LPS-stimulated IL-10 expression in ten renal transplant recipients.[5] IL-10 levels returned to normal after treatment with everolimus was completed.[5]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Immunosuppressive Activity

- The *in vitro* immunosuppressive activity of everolimus was less than that of rapamycin in a mixed lymphocyte reaction (IC_{50}: 0.2–1.6 versus 0.06–0.9 nmol/L) and in antigen-specific human helper T-cell clones (IC_{50}: 0.05–0.17 versus 0.014–0.037 nmol/L) [$p < 0.05$ for both comparisons].[3] Everolimus 10 and 100 nmol/L caused a significant and dose-dependent reduction in T-cell proliferation in cultures of anti-CD3–stimulated peripheral blood mononuclear cells from three healthy volunteers ($p < 0.05$ versus control).[6]
- Single doses of everolimus (0.75–17.5mg) in combination with ciclosporin and methylprednisolone significantly reduced T-cell proliferation in nine renal transplant recipients 2 and 6 hours after everolimus administration; proliferation returned to normal at 10 hours.[6]
- An analysis of exposure-response relationships in 695 renal transplant recipients treated with everolimus 0.75 or 1.5mg twice daily plus ciclosporin microemulsion and corticosteroids suggested a clear relationship for the risk of acute rejection and the everolimus blood trough concentration (C_{min}).[7] The lower immunosuppressive therapeutic threshold of everolimus in this study was 3 ng/mL; a significantly increased risk of acute rejection (approximately 3-fold) was observed when everolimus C_{min} values were less than 3 ng/mL compared with higher concentrations.[7]
- The immunosuppressive activity of oral everolimus 1–5 mg/kg/day was similar to that of rapamycin (at similar dosages) in rat models of renal or cardiac transplantation, localised graft-versus-host disease, and autoimmune glomerulonephritis.[3]

Synergistic Activity

- Synergistic activity between everolimus and ciclosporin has been demonstrated *in vitro* in a mouse mixed lymphocyte reaction and in rat models of orthotopic renal or heterotopic cardiac transplantation.[8] *In vivo*, the minimum effective dose for long-term (defined as graft survival of ≥100 days) allograft survival was ≥5 mg/kg for everolimus and 5 mg/kg for ciclosporin microemulsion in cardiac and renal transplantation models. However, when the two agents were combined, minimum effective doses of the two drugs were lower: everolimus 0.5 or 1.0 mg/kg and ciclosporin microemulsion 1.0 mg/kg were effective in achieving long-term survival of kidney and heart allografts.[8]
- A synergistic immunosuppressive effect was also demonstrated when everolimus was combined with FTY720 in a cardiac transplant model in rats.[9] As a single agent, everolimus 0.3, 1 and 3 mg/kg/day prolonged graft survival from a median of 6 days (with placebo) to 8.5, 18 and 37.5 days, respectively.[9] Similarly, FTY720 0.03, 0.1 and 0.3 mg/kg/day delayed rejection to 7, 9.5 and 15 days.[9] Combinations of everolimus 0.3 mg/kg/day plus FTY720 0.03 or 0.1 mg/kg/day prolonged median graft survival to 25 and 38.5 days. At the higher dosages of everolimus 1 mg/kg/day plus FTY720 0.03 or 0.1 mg/kg/day, median graft survival was prolonged to 42.5 and 43 days.[9]
- Similarly, a significant synergistic effect between everolimus and mycophenolate mofetil (MMF) was shown in a rat corneal transplantation model.[10] Exposure to everolimus 2.5 mg/kg/day or MMF 40 mg/kg/day resulted in a significant prolongation of graft survival to 25.5 ($p = 0.0001$) and 19.5 days ($p = 0.0053$) compared with the control group (12 days).[10] However, in combination, everolimus 1.5 mg/kg/day plus MMF 20 mg/kg/day resulted in significantly longer graft survival than achieved with the agents alone (100 days; $p = 0.03$ for both comparisons).[10]
- There was no evidence of an antagonistic effect between everolimus and tacrolimus in lymphocyte cultures stimulated with concanavalin A from renal transplant recipients.[11] The dose of everolimus in combination with tacrolimus 1 μg/L required to inhibit lymphocyte proliferation by 50% was similar to that of everolimus alone (27.1 versus 26.8 μg/L).[11]

Effects on Chronic Allograft Rejection

- Everolimus prevented chronic rejection in a model of chronic renal graft rejection in rats.[12] Rats

received everolimus 2.5 mg/kg/day or ciclosporin 1.5 mg/kg/day for 10 days after renal transplantation followed by everolimus 0.5 mg/kg/day or no treatment (control group).[12] At 24 weeks after transplantation, fewer animals receiving everolimus than control animals developed glomerulosclerosis (13.5 versus 24.5%; $p < 0.05$) and proteinuria was lower in animals exposed to everolimus than in the controls (11.6 versus 38.6 mg/day; $p < 0.01$).[12] Everolimus also significantly reduced the number of infiltrating macrophages and lymphocytes ($p < 0.01$).[12]

- The development of chronic rejection, as assessed by intimal thickening, was reduced by oral everolimus 0.31–1.25 or 2.5 mg/kg/day in rat models of vascular remodelling[13] or arteriosclerosis,[14] in which segments of aorta were subjected to cold ischaemia before transplantation. In contrast, ciclosporin microemulsion did not inhibit vascular remodelling.[13] Furthermore, everolimus inhibited atherosclerosis of transplanted carotid artery at dosages adequate to prevent rejection of transplanted heart transplants (0.3, 1.0 or 3.0 mg/kg/day) in severely hyperlipidaemic mice.[15]
- Everolimus 1.5 mg/kg/day in combination with ciclosporin and corticosteroids effectively prevented obliterative lesions in a porcine model of bronchial allograft[16] and inhibited epithelial destruction and airway remodelling in a pig heterotopic lung allograft model,[17] whereas a similar regimen with azathioprine 2 mg/kg/day instead of everolimus was ineffective in both studies. Everolimus 2.5 mg/kg/day and FTY720 0.3 mg/kg/day were both effective in the prevention of chronic rejection in a rat tracheal transplantation model.[18]

2. Pharmacokinetic Profile

The pharmacokinetic properties of oral everolimus 0.75 or 1.5mg twice daily have been investigated in renal[19,20] and cardiac[21] transplant recipients. The pharmacokinetic profile of everolimus, administered in combination with ciclosporin for 14 days, was not affected by varying degrees of renal function (mild to severe impairment) in 81 renal transplant recipients.[22] Therefore no adjustment to the everolimus dosage appears necessary for renal transplant recipients with early post-transplant renal impairment (section 6).[22]

Absorption and Distribution

- Oral everolimus 0.75 or 1.5mg twice daily (in combination with ciclosporin microemulsion and corticosteroids) exhibited approximately dose-proportional absorption kinetics after administration to renal transplant recipients for 6 months in a randomised, double-blind, multicentre trial.[19] Mean minimum blood everolimus concentration (C_{min}) values over the 6-month period were above the therapeutic threshold of 3 ng/mL for both dosages (4.3 and 7.2 ng/mL). At 6 months, mean maximum blood concentration (C_{max}) values were 10.7 and 21.1 ng/mL and mean area under the blood concentration-time curve (AUC) values were 76 and 138 ng • h/mL.[19] Everolimus was rapidly absorbed; median time to C_{max} (t_{max}) was 1 hour for both dosages at 6 months.[19]
- Intraindividual and interpatient variability in everolimus blood concentrations was observed in renal transplant recipients; however, sex, age or bodyweight did not account for the interpatient variability.[23]
- In cardiac transplant recipients treated with everolimus 0.75 or 1.5mg twice daily, C_{min} values over the 6-month period following transplantation (5.2 and 9.4 ng/mL) were also greater than the therapeutic threshold concentration.[21] C_{max} (10.2 and 20.7 ng/mL) and AUC (78 and 156 ng • h/mL) values at 6 months were also dose proportional.[21] Within-patient variability over 6 months for C_{min} and AUC was 38% and 30%.[21]
- When everolimus 2.5mg was administered with a high-fat meal (n = 6 renal transplant recipients), the rate of absorption was slower than that achieved in fasting conditions (median t_{max} 1 versus 2.8 hours); C_{max} was reduced by 53%, but the AUC was only slightly lower over the dosage interval (447 versus 378 ng • h/mL).[20] It is therefore recommended that everolimus be consistently administered either with or without food to avoid fluctuations in drug exposure over time (section 6).[20]

• At therapeutic concentrations, more than 75% of the everolimus dose is distributed into red blood cells and approximately 75% of the plasma fraction is bound to protein.[23] The tissue distribution of everolimus in humans has not yet been elucidated.

Metabolism and Elimination

• Incubation of everolimus with human liver microsomes *in vitro* led to the identification of 13 everolimus metabolites; the cytochrome P450 (CYP) enzymes 3A4, 3A5 and 2C8 were the major CYP enzymes involved in everolimus metabolism.[24]

• The metabolites identified in the blood of renal transplant recipients after oral administration of everolimus included hydroxy- dihydroxy-, demethyl- and the ring-opened forms of everolimus.[25-27] Hydroxy-everolimus is the main metabolite; its AUC_{24} was nearly half that of everolimus.[27]

• In renal transplant recipients, the elimination half-life ($t_{1/2}$) of everolimus after a single 0.75mg dose was 35 hours;[28] at steady state, $t_{1/2}$ values in recipients of 0.75 or 2.5 mg/day were 19.2 and 18.1 hours.[29] In healthy volunteers, the mean apparent clearance of everolimus after a single oral 2mg dose was 19.4 L/h.[30] In contrast, the apparent clearance of everolimus (dosage not reported) in a single renal transplant recipient was 8.8 L/h.[31]

Special Populations

Patients with Hepatic Impairment

• The apparent clearance of everolimus after a single 2mg dose was reduced by 53% in patients with moderate hepatic impairment (n = 8) compared with healthy volunteers (n = 8), resulting in a 115% higher AUC and a prolonged $t_{1/2}$ ($p < 0.05$ for all comparisons).[30] Thus, it is recommended that the everolimus dosage initially be halved in patients with mild or moderate hepatic impairment (section 6). The effect of severe hepatic impairment on the pharmacokinetic profile of everolimus has not been assessed; therefore, everolimus should be used with caution in this group (section 6).[30]

Ethnic Groups

• There appear to be ethnic influences on the clearance and/or bioavailability of everolimus.[19] After administration of everolimus 0.75 or 1.5mg twice daily, Black patients had an average 20% lower systemic exposure to everolimus compared with that in non-Black patients, indicating that Black patients may need a higher dosage of everolimus to achieve exposure similar to that in non-Black patients.[19] In contrast, Asian ethnicity did not significantly affect clearance.[31]

Drug Interactions

• Everolimus and ciclosporin are both metabolised by the CYP3A isoenzyme system and are substrates for P-glycoprotein; therefore, they have the potential to interact via competition for these pathways.[32] Thus, when combinations of everolimus and ciclosporin are used, therapeutic drug monitoring is likely to be required.

• Coadministration of single or multiple doses of everolimus 0.25–25mg with ciclosporin microemulsion for up to 12 months did not generally affect the steady-state pharmacokinetics of ciclosporin in renal transplant recipients.[23,27-29]

• In contrast, ciclosporin significantly altered the pharmacokinetic profile of everolimus in a single-dose study in healthy volunteers.[32] Coadministration of everolimus 2mg with ciclosporin microemulsion 175mg or ciclosporin USP 300mg resulted in a significant increase in everolimus exposure (168% and 74%; $p = 0.0001$) in 24 healthy volunteers.[32]

• Everolimus C_{min} values were significantly higher in the presence versus absence of ciclosporin.[33] Renal transplant recipients treated with everolimus 1.5mg twice daily, basiliximab and corticosteroids and ciclosporin (administered within 48 hours of transplantation; n = 40) had average everolimus C_{min} values approximately 3-fold higher than values in 16 patients with delayed graft function in whom ciclosporin treatment was delayed for 3–14 days (8.3 versus 2.9 ng/mL; $p < 0.001$).[33] However, everolimus C_{min} values were similar in the two treatment groups 1 month after transplantation.[33]

- The pharmacokinetic profile of everolimus (1.5mg twice daily) was similar in patients treated with either full-dose or a 35% reduced dose of ciclosporin microemulsion; patients also received basiliximab 20mg on days 0 and 4 and prednisone.[34]
- Renal transplant recipients receiving erythromycin, azithromycin or itraconazole (CYP3A inhibitors) in combination with everolimus (0.75 or 1.5 mg twice daily) had, respectively, a 22, 18 and 74% reduction in everolimus clearance.[31] Calcium channel blockers, quinolones and trimethoprim-sulfamethoxazole showed no effects on the pharmacokinetic profile of everolimus.[31]
- Coadministration of rifampicin 600 mg/day (a CYP3A enzyme inducer) with a single oral 4mg dose of everolimus in 12 healthy volunteers resulted in a significant 172% increase in the clearance of everolimus (statistical analysis not reported) and significant decreases in everolimus C_{max}, AUC and $t_{1/2}$ of 58, 63 and 26% ($p = 0.0001$ for all comparisons).[35]
- Coadministration of atorvastatin 20mg, a CYP3A4 substrate, or pravastatin 20mg, a P-glycoprotein substrate, with everolimus 2mg did not result in any clinically relevant drug interactions in a single-dose study in 24 healthy volunteers.[36]

3. Clinical Efficacy

The immunosuppressive efficacy of oral everolimus combined with full-dose ciclosporin microemulsion and corticosteroids in the prevention of allograft rejection has been assessed in randomised clinical trials in adult cardiac[37,38] or renal transplant recipients.[39-41] Limited data on the use of everolimus in combination with a reduced dosage of ciclosporin microemulsion[42] are also available. The majority of data are reported in abstracts;[38-42] however, one comparative trial has been published in full.[37]

Cardiac Transplant Recipients

A large, randomised, double-blind, double-dummy, multicentre trial assessed the efficacy of everolimus compared with that of azathioprine in 634 adult (aged 18–68 years) recipients of a primary cardiac transplant.[37] Patients who received a heart from a donor aged >60 years or with known heart disease were excluded. Pregnant women were also excluded.[37] Patient and donor characteristics, including age, weight, sex, race and primary reason for cardiac transplantation, were generally similar between treatment groups.[37]

Patients received oral everolimus 0.75 (n = 209) or 1.5mg (n = 211) twice daily or azathioprine 1–3 mg/kg/day (maximum dose 300 mg/day) [n = 214] for 12 months following transplantation.[37] All patients also received baseline immunosuppression with 'full-dose' ciclosporin microemulsion and corticosteroids and lipid-lowering therapy with pravastatin, simvastatin or fluvastatin.[37] Some patients also received induction therapy with antithymocyte globulin or muromonab CD3.[37]

The primary efficacy endpoint, efficacy failure, was a composite of the incidence of biopsy-confirmed acute rejection ≥ grade 3A (indicates the presence of multifocal inflammatory infiltrates and some damage to myocytes according to the International Society for Heart and Lung Transplantation criteria), rejection related to haemodynamic compromise, graft loss or retransplantation, death or loss to follow-up at 6 months.[37] Secondary endpoints included the proportion of patients with the primary endpoint at 12 months, the incidence of each of the individual components of this endpoint at 6 and 12 months, percentage of patients with acute rejection episodes treated with antibodies at 6 or 12 months, the incidence of allograft vasculopathy ('defined by an increase in the maximal intimal thickness of at least 0.5mm from baseline in at least one matched slice') 12 months after transplantation as assessed by intravascular ultrasound and the mean change in intimal thickness, intimal volume and intimal index (a measure of the area of stenosis) from baseline to 12 months.[37]

- Everolimus 0.75 or 1.5mg twice daily was significantly more effective than azathioprine in preventing acute graft rejection in cardiac transplant recipients at 6 months.[37] The incidence of the primary

composite endpoint, efficacy failure, was significantly lower in patients receiving everolimus 0.75 or 1.5mg twice daily than those receiving azathioprine 6 months after transplantation (36.4 and 27 versus 46.7%; $p = 0.03$ and $p < 0.001$).

- Similarly, the percentage of cardiac transplant recipients with efficacy failure 12 months after transplantation was significantly lower in those receiving everolimus 0.75 or 1.5mg in twice daily than in those receiving azathioprine (41.6 and 32.2 versus 52.8%; $p = 0.02$ and $p < 0.001$).[37] In addition, significantly fewer everolimus 0.75 or 1.5mg twice daily recipients experienced biopsy-confirmed acute rejection ≥ grade 3A 12 months after transplantation than those receiving azathioprine (30.6 and 21.3 versus 45.8%; $p < 0.001$ for both comparisons).[37] However, graft and patient survival rates at 12 months were similar for all treatment groups (data not reported).[37]

- Two years after transplantation, everolimus 0.75 or 1.5mg twice daily were more effective than azathioprine in reducing the incidence of efficacy failure in cardiac transplant recipients (45.9 and 36.0 versus 57.5%; $p = 0.016$ and $p < 0.001$). Moreover, the incidence of biopsy-confirmed acute rejection was significantly lower in those receiving everolimus 0.75 or 1.5mg twice daily than in azathioprine recipients (34.9 and 22.7 versus 48.1%; p-values not reported); however, there was no significant difference between the three treatment groups for patient survival at 2 years (90, 86.3 and 88.8%, respectively).[38]

- Everolimus 0.75 or 1.5mg twice daily was also more effective than azathioprine in reducing the incidence of vasculopathy in cardiac transplant recipients (35.7 and 30.4 versus 52.8%; $p < 0.05$ for both comparisons).[37] Intravascular ultrasound showed a smaller average increase in maximal intimal thickness from baseline at 12 months in patients receiving everolimus 0.75 or 1.5mg twice daily compared with azathioprine recipients (0.04 and 0.03 versus 0.10mm; $p = 0.01$ and $p = 0.003$).[37]

- The increase in mean maximal intimal thickness 2 years after transplantation was significantly lower in patients receiving everolimus 0.75 or 1.5mg twice daily than in those receiving azathioprine (0.07 and 0.06 versus 0.15mm; $p < 0.05$ and $p < 0.01$).[38] Additionally, the incidence of graft vasculopathy (maximum intimal thickness increase ≥0.5mm) 2 years after transplantation was significantly lower in patients receiving everolimus 0.75mg twice daily than in recipients of azathioprine (33.3 versus 58.3%; $p < 0.05$), but not for recipients of everolimus 1.5mg twice daily (45.5%).[38]

Renal Transplant Recipients

The efficacy of everolimus for the prevention of acute allograft rejection after renal transplant has been compared with that of MMF in two large, randomised, double-blind, multicentre trials in 583[39] and 588[40] *de novo* renal transplant recipients. One study was conducted in North and South America[39] and the other was an international study.[40] Renal transplant recipients were randomised to receive everolimus 1.5 or 3 mg/day or MMF 2 g/day.[39,40] All patients also received full-dose ciclosporin microemulsion and corticosteroids as baseline immunosuppression (dosages not reported).[39,40] Long-term (3-year) data are also available for the international trial.[41]

- Everolimus 1.5 or 3 mg/day was as effective as MMF 2 g/day in preventing graft rejection in these two large clinical trials.[39,40] There were no significant differences between those receiving everolimus 1.5 or 3 mg/day and those receiving MMF 2 g/day for the incidence of the primary composite endpoint (biopsy-confirmed acute rejection, graft loss, death, or loss to follow-up) 12 months after transplantation in both clinical trials (figure 1).[39,40]

- The combined incidence of graft loss or patient death at 12 months or the incidence of biopsy-confirmed acute rejection 6 months after transplantation was similar for those receiving everolimus 1.5 or 3 mg/day or MMF in both clinical trials.[39,40] Patient survival at 12 months was ≥95% in all treatment groups in both clinical trials.[39,40]

- The incidence of antibody-treated acute rejection at 6 months was significantly lower with everolimus 1.5 mg/day compared with MMF 2 g/day in the trial conducted in North and South America (7.3 versus

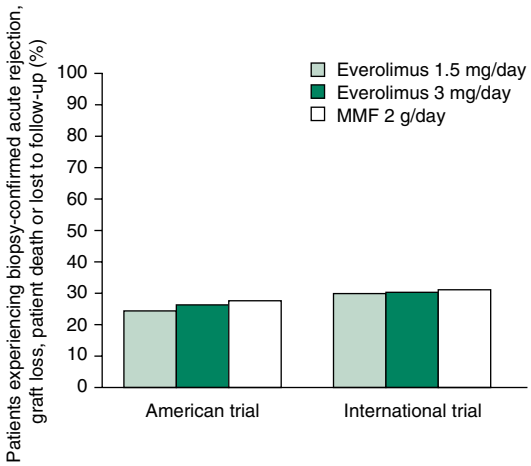


Fig. 1. Comparative efficacy of everolimus and mycophenolate mofetil (MMF) for the composite endpoint (biopsy-confirmed acute rejection, graft loss, death, or loss to follow-up) 12 months after transplantation in adult *de novo* renal transplant recipients.[39,40] In two (one American[39] and one international[40]) randomised, double-blind, multicentre clinical trials (n = 583;[39] n = 588)[40] patients received everolimus 1.5 or 3 mg/day or MMF 2 g/day in combination with ciclosporin microemulsion and corticosteroids (dosages not reported).

15.3%; p = 0.009).[39] However, there was no significant difference in the incidence of antibody-treated acute rejection 6 months after transplantation between those receiving everolimus 1.5 or 3 mg/day and those receiving MMF 2 g/day in the international study (6.7, 6.6 and 7.2%, respectively).[40]

- The incidence of the composite endpoint (biopsy-confirmed acute rejection, graft loss, death or loss to follow-up) 3 years after transplantation was similar in patients treated with everolimus 1.5 or 3 mg/day or MMF 2 g/day in the international trial (33.0, 38.9 and 37.2%, respectively).[41] However, the incidence of late-occurring (between 2 and 3 years) biopsy-confirmed acute rejection, graft loss, death, or loss to follow-up was significantly lower in recipients of everolimus 1.5 mg/day than in those receiving everolimus 3 mg/day or MMF 2 g/day (1.2 versus 7.3 and 5.9%, respectively; p-values not reported).[41]

- The incidence of patient death at 3 years was similar in the everolimus 1.5 mg/day, everolimus 3 mg/day or MMF 2 g/day treatment groups in the international trial (8, 9 and 8%).[41] Graft loss at 3 years was also similar in recipients of everolimus 1.5 mg/day or MMF 2 g/day (7.2 and 10.7%), but was significantly higher in those receiving everolimus 3 mg/day (16.7%; p-value not reported).[41]

- Preliminary data are available from a randomised, open-label, multicentre trial in 111 adult renal transplant recipients receiving everolimus 3 mg/day, basiliximab 20mg on days 0 and 4 and corticosteroids in combination with full- or reduced-dose ciclosporin microemulsion.[42] The incidence of biopsy-confirmed acute rejection, graft loss or patient death 12 months after transplantation was significantly lower in patients receiving everolimus in combination with reduced-dose ciclosporin microemulsion than in those receiving the full-dose regimen (data and statistical analysis not reported).[42]

4. Tolerability

This section provides a summary of tolerability data from the clinical trials that evaluated everolimus as part of a combination immunosuppression regimen in patients who had undergone cardiac or renal transplantation (section 3).

- Everolimus was generally well tolerated in cardiac transplant recipients.[37] The incidence of premature discontinuation of the study drug due to adverse events was similar for those receiving everolimus 0.75 or 1.5mg twice daily or azathioprine (15.8, 21.8 and 13.1%).[37] The most common reasons for the premature discontinuation of study drug due to adverse events were renal disorders, infections, leucopenia, gastrointestinal disorders, neurological disorders, anaemia and thrombocytopenia.[37] There was no significant difference between the three treatment groups in the incidence of each event.[37]

- Compared with azathioprine, recipients of everolimus 0.75 or 1.5mg twice daily had a significantly lower incidence of overall viral infection (including cytomegalovirus [CMV], herpes simplex and herpes zoster) [14.8 and 17.1 versus 31.3%; p < 0.001 for both comparisons] and CMV infection (7.7 and 7.6 versus 21.5%; p < 0.001 for both comparisons) 12 months after cardiac transplantation.[37] Conversely, the incidence of bacterial infections at 12 months was significantly higher in patients receiving ever-

olimus 1.5mg twice daily than in those receiving azathioprine (37.9 versus 24.8%; p = 0.001).[37]

- The incidence of CMV infection remained significantly lower in patients receiving everolimus 0.75 or 1.5mg twice daily than in azathioprine recipients 2 years after cardiac transplantation (8.6 and 8.1 versus 22.4%; p-values not reported).[38] However, the incidence of bacterial infections at 2 years was significantly higher in patients receiving everolimus 0.75 or 1.5mg twice daily than in those receiving azathioprine (37.3 and 40.3 versus 22.4%; $p < 0.05$ for both comparisons).[38]
- In the international trial in renal transplant recipients, the incidence of CMV infection was significantly lower in those receiving everolimus 1.5 or 3 mg/day than in recipients of MMF at 12 months (5.2 and 7.6 versus 19.4%; $p < 0.05$ for both comparisons)[40,43] and 3 years after transplantation (6 and 7 versus 20%; p-values not reported).[41]
- Everolimus has been associated with thrombocytopenia and leucopenia in cardiac and renal transplant recipients.[44] Dose-related reductions in platelet counts occurred more frequently in renal transplant recipients receiving everolimus than in those receiving MMF.[40,41] The mean platelet count at 12 months was significantly lower in cardiac transplant recipients receiving everolimus 1.5mg twice daily than in those receiving everolimus 0.75mg twice daily or azathioprine (213 versus 225 and 233 $\times 10^{-3}/mm^3$; p = 0.001 for both comparisons); however, the mean leucocyte count was similar for the three treatment groups at 12 months.[37]
- Dose-related elevations in serum lipid levels were observed more frequently in renal transplant recipients receiving everolimus 1.5 or 3 mg/day than in those receiving MMF (data not reported).[40,41] Increases in serum lipid levels in renal transplant recipients peaked at 2 months and were responsive to lipid-lowering therapy.[39,40]
- Similarly, significantly more cardiac transplant recipients receiving everolimus 0.75 or 1.5mg twice daily had elevated mean total cholesterol (62.8 and 66.8 versus 45.8%) and triglyceride levels (26.6 and 32.7 versus 14.5%) than those receiving azathioprine (p = 0.01 for all comparisons; timepoint not reported).[37] However, the ratio of low-density lipoprotein (LDL) to high-density lipoprotein (HDL) cholesterol was similar in those receiving everolimus 0.75 or 1.5mg twice daily or azathioprine.[37] Two years after transplantation, serum lipids (triglycerides and cholesterol) were elevated in everolimus recipients ($p < 0.05$); however, there were no between-group differences in mean LDL and HDL cholesterol levels.[38]
- Renal transplant recipients receiving everolimus had a higher incidence of increased serum creatinine levels than MMF recipients when administered with full-dose ciclosporin microemulsion.[39,40] Mean creatinine values were higher in patients receiving everolimus 1.5 or 3 mg/day than those receiving MMF (165 and 199 versus 146 μmol/L; timepoint and statistical analysis not reported); however, from 1 to 3 years the mean creatinine and creatinine clearance values improved in all treatment groups.[41]
- Similarly, in cardiac transplant recipients receiving full-dose ciclosporin microemulsion, median serum creatinine levels were significantly higher in those receiving everolimus 1.5mg twice daily than in recipients of azathioprine 1–3 mg/kg/day or everolimus 0.75mg twice daily at 28 days after transplantation (142 versus 117 and 124 μmol/L; p = 0.01 and p = 0.001)[37] and remained significantly higher in everolimus recipients at 2 years ($p < 0.05$).[38] Two years after cardiac transplantation in patients receiving full-dose ciclosporin, the incidence of chronic renal failure was 3.8% in patients receiving everolimus 0.75 or 1.5mg twice daily and 0.9% in recipients of azathioprine.[45]
- Limited data are available on the tolerability of everolimus 3 mg/day in combination with a reduced-dose ciclosporin microemulsion regimen in renal transplant recipients.[42] Increases in cholesterol and triglyceride levels were observed in patients receiving everolimus in combination with both full- or reduced-dose ciclosporin microemulsion; however, these increases were more pronounced in patients receiving the full-dose regimen.[42] Adverse events associated with drug toxicity and discontinuation of the study drug due to adverse events were

more common in patients receiving full-dose ciclosporin microemulsion.[42]

5. Pharmacoeconomic Considerations

Two prospective economic evaluations have been performed using clinical data from comparative clinical trials in cardiac[37] or renal transplant recipients[40] (section 3); both are available as abstracts.[46,47] Costs from the clinical trial in cardiac transplant recipients were converted to US dollars (2001 currency year) using Organisation for Economic Co-operation and Development Purchasing Power Parity rates;[46] costs from the international trial in renal transplant recipients were also converted to US dollars, although the currency year was not reported.[47]

- The mean total costs of treatment (excluding the cost of study drugs) over 12 months were similar in cardiac transplant recipients receiving everolimus 1.5 or 3 mg/day or azathioprine ($US76 160, $US75 519 and $US73 495).[46] Similarly, there was no significant difference in the mean cost of treatment (excluding the cost of study drugs) in renal transplant recipients receiving everolimus 1.5 or 3 mg/day or MMF ($US33 715, $US38 519 and $US36 509).[47]
- The incremental costs per cardiac transplant recipient free from efficacy failure with everolimus 1.5 or 3 mg/day compared with azathioprine was $US24 851 and $US10 062, respectively.[46] The costs per renal transplant recipient free of biopsy-confirmed acute rejection, graft loss, death, or loss to follow-up with everolimus 1.5 or 3 mg/day or MMF were $US48 093, $US55 266 and $US53 005.[47]

6. Dosage and Administration

Everolimus is indicated for the prophylaxis of organ rejection in adult patients, at low-to-moderate immunological risk, receiving a renal or cardiac transplant. The drug should be administered in combination with ciclosporin microemulsion and corticosteroids.[48] It is recommended that everolimus be administered orally at an initial dosage of 0.75mg twice daily as soon as possible after transplantation.[48] Everolimus should be administered consistently with or without food (in order to avoid variations in drug exposure over time) at the same time as ciclosporin microemulsion.[48]

There is no need to adjust the dosage of everolimus for patients with renal impairment (section 2).[48] However, it is recommended that the everolimus dose initially be halved in patients with mild or moderate hepatic impairment if two of the following apply: bilirubin >34 μmol/L, albumin <35 g/L, prothrombin time >4 second prolongation.[48] The effect of severe hepatic impairment on the pharmacokinetic profile of everolimus has not been assessed; therefore, everolimus should be used with caution in these patients (section 2).[48] Limited data suggest that Black patients may require a higher dosage of everolimus to achieve similar efficacy to non-Black patients (section 2). However, specific recommendations for use in Black patients are not currently available.[48]

Routine everolimus whole blood therapeutic drug level monitoring is recommended.[48] Renal and cardiac transplant recipients with everolimus whole blood trough concentrations ≥3.0 ng/mL had a lower incidence of biopsy-confirmed acute rejection than those with trough concentrations <3.0 ng/mL (section 1).[48] The upper limit of the therapeutic range is 8 ng/mL; blood everolimus concentrations above 12 ng/mL have not been investigated.[48] It is important to monitor everolimus blood concentrations in patients with hepatic impairment, during concomitant administration of CYP3A4 inducers and inhibitors, when switching everolimus formulations or if the dosage of ciclosporin is markedly reduced.[48]

Everolimus should not be used together with full-dose ciclosporin long term. Reduced exposure to ciclosporin in everolimus recipients improves renal function.[48] Reduction in ciclosporin exposure should be started after 1 month post-transplantation.[48]

7. Everolimus: Current Status

Everolimus has been approved in the EU for use in the prevention of rejection in adult cardiac or

renal transplant recipients.[49] It has also been submitted for approval in the US. Everolimus has shown efficacy in the prevention of graft rejection in well-designed trials in adult cardiac and renal transplant recipients and was generally well tolerated.

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Correspondence: *Caroline M. Perry*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz