



**Clinical Commissioning
Policy Proposition:
Everolimus for prevention
of organ rejection following
heart transplantation**

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Clinical Commissioning Policy Proposition: Everolimus for prevention of organ rejection following heart transplantation

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Equality Statement

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Plain Language Summary

Heart transplant is a treatment option for patients with end-stage heart disease, the final phase of the disease when there is no other effective medical or surgical treatment. Following the transplant, patients will need anti-rejection drugs to prevent their immune system attacking and rejecting the heart. However, this also puts the patient at risk of infection. Strategies to prolong the transplanted heart's survival, and the survival of the patient following transplant are priorities in heart transplant.

Everolimus is an anti-rejection drug that has been proposed for use for treatment following heart transplant. It works by blocking of the signal of anti-bodies, the body's defence system, to stop the anti-bodies growing and dividing at the first stage of the cell cycle, preventing rejection of the transplanted heart.

There are a number of immunosuppressants available, however their side effects can be an issue. Therefore having different combinations available helps to minimise some of these side effects to achieve the best combination for the patient.

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of everolimus for immune suppression for the prevention or reduction of organ rejection and kidney dysfunction in patients at risk following heart transplant.

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1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission everolimus for prevention of organ rejection following heart transplant.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether everolimus for prevention of organ rejection following heart transplant will not be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

Allogeneic cardiac transplantation is the transfer of the heart organ from a donor to the host patient. Following the procedure, patients will need immunosuppressants to suppress their immune system and prevent it from attacking and rejecting the heart. These immunosuppressants put the patients at risk of infection and adverse drug effects.

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor that exerts an immunosuppressive effect by inhibiting the proliferation, and thus clonal expansion, of antigen-activated T cells. Everolimus causes immunosuppression via different pathways to other treatments, and has been proposed as an alternative immunosuppressant treatment to prevent organ rejection and kidney dysfunction in patients at immunological risk following an allogeneic cardiac transplant.

3. Definitions

Allogeneic cardiac transplantation is the transfer of the heart organ from a donor to the host patient. Cardiac transplantation has emerged as a viable therapeutic strategy for selected patients with end-stage heart disease, offering extended survival and improved quality of life. Following the procedure, patients will need immunosuppressants to suppress their immune system and prevent it from attacking and rejecting the heart. These immunosuppressants put the patients at risk of infection and adverse drug effects.

Everolimus, a proliferation signal inhibitor, exerts an immunosuppressive effect by inhibiting the proliferation, and thus clonal expansion, of antigen-activated T cells. Everolimus inhibits an intracellular signalling pathway which is triggered upon binding of these T cell growth factors to their respective receptors, and which normally leads to cell proliferation. The blockage of this signal by everolimus leads to an arrest of the cells at the G1 (first) stage of the cell cycle, preventing allograft rejection.

The effect of everolimus is not restricted to T cells. It inhibits in general, growth factor-stimulated proliferation of haematopoietic as well as non-haematopoietic cells, such as those of vascular smooth muscle cells. Growth factor-stimulated vascular smooth muscle cell proliferation, triggered by injury to endothelial cells and leading to neointima formation, plays a key role in the pathogenesis of chronic rejection. Preclinical studies with everolimus have shown inhibition of neointima formation in a rat aorta allotransplantation model.

4. Aim and objectives

This policy proposition aims to define NHS England's commissioning position on everolimus as part of the treatment pathway for immune suppression in adult and paediatric patients post allogenic cardiac transplant.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adult and paediatric patients post allogenic cardiac transplant.

5. Epidemiology and needs assessment

In 2014/15, there were 181 adult and 37 paediatric heart transplants performed across England (NHS Blood and Transplant, 2015).

Severe renal failure (CKF grade 4 or 5), defined as estimated Glomerular Filtration Rate (eGFR) <30ml/min, affects approximately 4.65% and 9% of patients at three years and five years post heart transplant (NHS Blood and Transplant, 2015). Based on 2013/14 data, approximately 10 patients would suffer severe renal failure at three years post transplant, and 20 patients at five years post transplant. Clinicians have estimated there is a large "iceberg" of patients with significant renal impairment as a result of calcineurin inhibitors (CNIs), who have not reached the stage of dialysis, but whose whole management is very difficult. Chronic renal failure is associated with heightened risk of cardiovascular disorder and other concomitant conditions. Post transplant patients with chronic renal failure are also at heightened risk of death.

Cardiac allograft vasculopathy (CAV) occurs in >40% of heart transplant patients within 5 years of surgery. Patients with CAV have significantly reduced survival time compared to patients without CAV.

Patients with these indications would be suitable for treatment with everolimus.

6. Evidence base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of everolimus for prevention of organ rejection following heart transplant.

Following a heart transplant (HT), calcineurin inhibitors (CNIs), such as cyclosporine or tacrolimus, are administered in order to reduce the risk of graft loss or acute rejection. CNI exposure is considered to play a key role in renal damage that can cause long term fatal renal failure, although renal failure is not the most common cause of death following HT. Mortality in the first year post-HT is primarily caused by graft failure and infection. Mortality from malignancy and cardiac allograft vasculopathy (CAV) predominates in subsequent years. To improve survival rates and reduce side effects, antiproliferation agents, such as azathioprine and mycophenolate mofetil (MMF), can be used in combination with CNIs. CNIs form the backbone of immunosuppression but are part of a standard triple therapy

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regimen together with an antimetabolite (MMF or azathioprine) and steroids.

The proliferation signal inhibitors sirolimus or everolimus can be used as an alternative to antiproliferation agents i.e. in combination with CNI or as an alternative to CNIs in combination with an antiproliferative agent (e.g. renal sparing strategy). Hence the clinical efficacy and specific advantages of everolimus can be measured in terms of the efficacy in reducing organ rejection or death, impact on renal function, rates of adverse effects (in particular CMV infections), in addition to the treatment and prevention of CAV.

This literature review was aimed at identifying the current evidence for everolimus post cardiac transplant, specifically to answer the following questions:

1. Is everolimus, in combination with other drugs, clinically effective in preventing organ rejection and adverse effects post cardiac transplant?
2. Does everolimus, in combination with other drugs, offer specific advantages in terms of organ rejection and adverse effects?
3. Is everolimus a cost-effective treatment option for preventing organ rejection and adverse effects post cardiac transplant?

This review found:

- There is level 1 evidence that everolimus, and a reduced cyclosporine dose, is not inferior to MMF and superior to azathioprine in preventing organ rejection. However, everolimus alone is inferior to treatments with cyclosporine.
- There is level 1 evidence that everolimus helps to prevent CAV, but there is no evidence that it is effective against established CAV.
- There is level 1 evidence that everolimus is associated with a reduced CMV infection rate, compared with azathioprine and MMF.
- The evidence that everolimus and a reduced CNI dose results in an improved renal function is conflicted and is likely to be sensitive to the precise details of the CNI dose.
- There is level 1 evidence that everolimus treatment strategies are associated with a reduced risk of leukopenia, but an increased risk of pneumonia and pericardial effusion, when compared with MMF treatments. Overall, during treatment with everolimus a higher number of serious non-fatal adverse events are recorded.

1a. Clinical effectiveness of everolimus in preventing organ rejection post cardiac transplant

The principle outcome for measuring the clinical effectiveness in preventing organ rejection is the rate of biopsy proven acute rejection (BPAR), graded according to international society of heart and lung transplants grading (ISHLT) systems. It is also possible to look at rates of graft loss, death or a composite endpoint (defined as BPAR \geq 3A, graft loss or death).

- There is level 1 evidence, from 1 large RCT (n=553) with 24 month follow up, that 1.5 mg/day of everolimus with a reduced cyclosporine dose has a statistically similar acute rejection rate to 3 g/day of MMF with a standard cyclosporine dose (24% vs 27%) (Eisen et al., 2013).
- There is level 1 evidence, from 1 large RCT (n=634) with 24 months follow up, that a treatment of everolimus (1.5mg/day) has a lower rate of acute rejections (BPAR \geq 3A) than a treatment of Azathioprine (34.9% vs 48.1%, p=0.005), with both treatments using a standard cyclosporine dose. The acute rejection rate improved further with 3.0mg/day of

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everolimus (22.7%). However, subsequent trials with 3.0mg/day of everolimus were halted by the data monitoring committee due to a perceived high mortality rate. The rates of graft loss and death were statistically similar (Vigano et al., 2007).

- A smaller RCT (n=115) found that a treatment schedule including everolimus and MMF, in which the use of CNIs was withdrawn after 7-11 weeks, led to an increase in the acute rejection rate, compared with the use of MMF and cyclosporine (43% vs 15%, $p<0.01$), (Arora et al., 2015). This result was in agreement with a level 2+ cohort study that found the acute rejection rate for everolimus with a reduced cyclosporine dose was lower than everolimus with no cyclosporine (Gonzalez-Vilchez et al., 2014).

1b. Clinical effectiveness of everolimus in preventing and treating CAV post cardiac transplant

While the rate of CAV is sometimes recorded, it is more productive to measure the impact of treatment schedules on CAV by using an intravascular ultrasound to measure the change, from baseline value, in the coronary maximal intimal thickness (Δ MIT). An incidence of CAV is often defined as Δ MIT \geq 0.5mm. Other metrics, such as the change in atheroma volume and intimal area, typically mirror the Δ MIT results.

The same two large RCTs and one small RCT all found respectively that 1.5 mg/day everolimus resulted in:

- A Δ MIT=0.07mm compared with azathioprine, Δ MIT=0.15mm, $p=0.014$, after 24 months. (Vigano et al., 2007)
- A Δ MIT=0.03mm compared with MMF, Δ MIT=0.07mm, $p<0.001$, after 12 months (Eisen et al., 2013).
- A Δ MIT=0.03mm compared with MMF, Δ MIT=0.08mm, $p=0.02$, after 12 months (Arora et al., 2015).

This resulted in rates of CAV for everolimus of between (12%-33%) vs. (27% - 58%) for azathioprine and MMF treatments.

However, this was based on using everolimus from the first month post-HT, to prevent CAV. A different RCT (n=111) examined the impact of everolimus on patients, an average of 5.8 years post-HT, who had established CAV (mean baseline MIT = 0.56mm). Both the everolimus and MMF arm found no impact on the CAV, Δ MIT=0.0 \pm 0.04mm and Δ MIT=0.04 \pm 0.04mm respectively (Arora et al., 2011). Likewise, a retrospective cohort study (n=143) found that everolimus and MMF had no impact on MIT between 1 year post HT and 5 year post HT (Masetti et al., 2013).

1c. Clinical effectiveness of everolimus in preventing CMV infection post cardiac transplant

There is level 1 evidence that everolimus is associated with a lower incidence of CMV infection. There is good agreement from four RCTs (Eisen et al., 2013 n=553 plus three combined in a meta-analysis in Kobashigawa et al., 2013, n=1009) and one large cohort study (Durante-Mangoni et al., 2015, n=378). It is found that the CMV infection rate, when the treatment strategy is using everolimus is between 3-9%. Whereas when azathioprine or MMF is used, this rises to between 19-33%.

2a. Advantages of everolimus, in combination with other drugs, in terms of nephrotoxicity

Renal function can be assessed using creatine clearance or measured/estimated glomerular filtration rates (m/eGFR), all based on creatine concentrations. Although, it was argued in (Stypmann et al., 2015) that deterioration in renal function can occur prior to an increase in serum creatine level. Hence they argue for using Neutrophil gelatinase-associated lipocalin (NGAL) levels.

- During a large RCT (n=553), eGFR was found to indicate that 1.5mg/day of everolimus with a reduced cyclosporine dose was inferior to MMF and a standard dose of cyclosporine (a mean change from baseline of eGFR of -0.67 mL/min/1.73 m² vs 1.6 mL/min/1.73 m²). However, closer examination revealed that this difference occurred in the first 3 months post HT, when both treatments had similar cyclosporine doses (Eisen et al., 2013).
- A small RCT (n=115), which used everolimus and no cyclosporine after week 11 compared with MMF and cyclosporine, found that the everolimus arm had a significantly higher mGFR (79.8 mL/min/1.73 m² vs 61.5 mL/min/1.73 m², p<0.001) after 12 months. Although the same trial reported a higher rate of acute rejections for the everolimus arm (Andreassen et al., 2014).
- Two further RCTs and a Cohort study (n=176, n=70 & n=121) compared everolimus with a reduced cyclosporine dose and MMF with a standard cyclosporine dose. After 12 months no difference in the creatine clearance levels was found in the two RCTs. Although, the everolimus arm had lower levels, but the sample size stopped this from being statistically significant (Lehmkuhl et al., 2009; Bara et al., 2013). The cohort study found plasma and urine NGAL levels significantly lower in the everolimus cohort (p<0.001), favouring the everolimus treatment strategy (Stypmann et al., 2015).

2b. Advantages of everolimus, in combination with other drugs, in terms of adverse effects

In addition to CMV infection there were a large number of additional adverse effects reported during these trials. The majority had similar rates between the respective treatment strategies, but it is worth commenting on the differences. In particular:

- (Eisen et al., 2013 and Lehmkuhl et al., 2009) both reported that everolimus treatment strategies had a lower rate of Leukopenia than MMF, (13-16% vs 26-30%, p=0.011).
- (Eisen et al., 2013) reported that everolimus was associated with higher rates of pericardial effusion than MMF (44% vs 29%, p<0.001).
- Overall patients treated with everolimus had more nonfatal serious adverse events than those treated with MMF (74.2% vs 61.2%), (Eisen et al., 2013).
- (Vigano et al., 2007) reported that treatment with everolimus resulted in higher rate of pneumonia than azathioprine (13.9% vs 2.8% p<0.001).

3. Cost effectiveness of everolimus in preventing organ rejection and adverse effects post cardiac transplant

Two studies were found that looked at the cost effectiveness of everolimus treatments. The first compared the total cost of everolimus and azathioprine, with both treatments aiming for standard doses of cyclosporine. The study found that everolimus was marginally more expensive, \$72,065 vs \$70, 815 (£47,910 v £47,079) . This difference was primarily due to

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increased hospitalisation costs and secondarily due to increased concomitant medication costs, although there were savings made on the cyclosporine costs (Radeva et al., 2005). The second study was based on the German health care model and looked at the incremental cost of everolimus and MMF verses azathioprine divided by the reduction in efficacy failure (the incremental cost effectiveness ratio ICER). The study favoured everolimus over MMF with an ICER of 24,457 Euros vs 29,912 Euros (£17,593 v £21,516), although the study doesn't appear to include hospitalisation costs (Annemans et al., 2007).

7. Documents which have informed this policy proposition

Not applicable.

8. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).