tacrolimus, 5mg/ml concentrate for infusion and 0.5mg, 1mg, 5mg hard capsules (Prograf®) No. (346/07)

Astellas Pharma Ltd

12 January 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

tacrolimus (Prograf®) is accepted for restricted use within NHS Scotland for the prophylaxis of transplant rejection in heart allograft recipients.

It has shown comparable efficacy to ciclosporin-based regimens in prevention of acute rejection. It is restricted to use in patients where ciclosporin is not suitable.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Prophylaxis of transplant rejection in heart allograft recipents.

Dosing information

Tacrolimus can be used with antibody induction (allowing for delayed start of tacrolimus therapy) or alternatively in clinically stable patients without antibody induction.

Following antibody induction, oral tacrolimus therapy should commence at a dose of 0.075 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 5 days after the completion of surgery as soon as the patient's clinical condition is stabilised. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.01 to 0.02 mg/kg/day should be initiated as a continuous 24-hour infusion.

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Date of licensing

1 June 2006

Product availability date

1 June 2006

Summary of evidence on comparative efficacy

Eight open-label studies assessed tacrolimus-based regimens in adult patients receiving a heart transplant. Patients with previous transplants and those awaiting multiple transplants were excluded. Regimens fell into two broad categories. Three studies compared tacrolimus or ciclosporin in combination with mycophenolate mofetil (MMF) and corticosteroids, while in the remaining five studies tacrolimus or ciclosporin was combined with azathioprine and corticosteroids. The regimens used in individual studies varied widely, but common features are described in the clinical effectiveness section.

Rejection was graded according to diagnostic criteria from the International Society for Heart and Lung Transplantation (ISHLT) developed in 1990 and simplified in 2004 to none, mild, moderate and severe. These are based on cellular signs of rejection on endomyocardial biopsy and do not take account of humoral (antibody-mediated) signs of rejection.

In combination with MMF and corticosteroids

In the largest study in this category, 334 patients were randomised to tacrolimus in combination with either MMF or sirolimus, or to ciclosporin and MMF. All patients also received corticosteroids. The primary end-point was the incidence of moderate to severe acute rejection or haemodynamic compromise requiring therapy within 6 months post-transplant. This occurred in 22% of patients in the tacrolimus/MMF group, 24% in the tacrolimus/sirolimus group and 32% in the ciclosporin/MMF group. There was no significant difference among groups (p=0.271).

There was a significant difference in favour of tacrolimus/MMF (over ciclosporin/MMF) in the 12-month incidence of acute rejection as defined above (23% vs 37%, p=0.029) and in the incidence of any treated rejection at 1 year (42% vs 60%, p=0.009). Patient and graft survival

at one year was 95% in the tacrolimus/MMF group, 91% in the tacrolimus/sirolimus group and 90% in the ciclosporin/MMF group with no significant difference between groups.

In another study, 60 patients were randomised to tacrolimus/MMF or ciclosporin/MMF, both with corticosteroids, and freedom from acute rejection by Kaplan-Meier analysis was significantly higher in the tacrolimus group than in those receiving ciclosporin (p=0.0001). In this study, patients were to be followed up for two years and the definition of rejection would include some patients with a mild grade of rejection, with or without clinical signs or symptoms requiring treatment.

In a study designed to investigate ethnic differences in response (n=63), significantly more tacrolimus-treated black American patients were free from acute rejection that required treatment at one year post-transplant compared to black Americans treated with ciclosporin (64% vs 37%, p=0.01); no significant difference was observed between tacrolimus-treated black Americans and whites (64% and 67% respectively).

In combination with azathioprine and corticosteroids.

The largest study in this category (n=314) compared tacrolimus- and ciclosporin-based oral regimens started during antibody induction. For the primary end-point the definition of rejection included some patients with mild grade rejection. The incidence of first rejection within the first 6 months post-transplant, when assessed by a blinded central biopsy assessment, was significantly lower in the tacrolimus-treated patients than in those assigned to ciclosporin (54% vs 66%, p=0.029), though the difference was not significant for non-blinded assessments performed locally. The 6-month incidence of moderate to severe rejection was significantly lower in the tacrolimus-based therapy group than in the ciclosporin-based therapy group (28% vs 42%, p=0.013).

The Kaplan-Meier estimate of patient/graft survival rate was 93% for tacrolimus and 92% for ciclosporin at 1 year. At 18 months the survival estimate was unchanged for the tacrolimus group and was 90% for ciclosporin, with no significant difference between the groups (p=0.35).

Another study provides results from 67 patients at 5 years post-transplant. Rates of moderate to severe rejection were not significantly different between patients treated with tacrolimus and those receiving ciclosporin (76% vs 79%, p=0.73). Results were also comparable between groups for rates of freedom from any treated rejection (70% vs 68% respectively, p=0.53); patient survival rates at 5 years (79% vs 71%, p=0.39) and the incidence of cardiac allograft vasculopathy at 5 years, determined by annual angiography (54% vs 64%, p=0.42).

In a European multi-centre pilot study, and in a single-centre study which ran in parallel with it, (n=82 and 73 respectively), freedom from acute rejection at 12 months (as estimated by the Kaplan-Meier method) was numerically higher in the tacrolimus group compared to the ciclosporin group in the first study and lower in the second, but neither difference was statistically significant.

In a further study, randomisation was stratified according to the risk of developing severe post-operative renal insufficiency in order to standardise the use of peri-operative anti-lymphocyte antibody therapy. Those classified as 'low-risk' were treated with pre-operative tacrolimus or ciclosporin: in those at 'high risk' this therapy was delayed until 3 days post-transplantation and antibody induction therapy was given peri-operatively. All patients were treated with peri-operative azathioprine and corticosteroids. Eighty-five patients at six cardiac transplant centres were enrolled in the study. Thirty-nine patients were randomised to receive tacrolimus-based therapy and 46 patients were randomised to receive ciclosporin-based therapy. The probability of remaining free from moderate to severe acute rejection by 6 months was 0.45 for the tacrolimus group and 0.56 for ciclosporin (unadjusted p=0.46; p=0.3 after adjusting for centre and patients' status relating to urgency of transplantation). Tacrolimus was also comparable to ciclosporin with regard to the probability of remaining free from any treated rejection episode, with no significant difference between the two treatment groups (p=0.54). Similarly, no significant differences were evident in freedom from rejection when defined so as to include some patients with mild rejection.

Summary of evidence on comparative safety

The most frequent adverse events observed in the tacrolimus trials were renal disorders, glucose metabolism disorders, hypertension, dyslipidaemia and infections.

The incidence of renal dysfunction was comparable between the tacrolimus and ciclosporin groups in the majority of trials including the two largest trials, although in one of these the median serum creatinine levels were significantly lower in the tacrolimus/MMF group than in the ciclosporin/MMF group.

There was no statistically significant difference between treatment groups in the incidence of new onset diabetes except that it occurred more frequently in the tacrolimus group compared to the ciclosporin group in the largest of the trials involving combination with azathioprine (20.3% vs. 10.5%; p=0.038).

In the majority of trials where it was reported, including the two largest trials, dyslipidaemia was more frequent in patients treated with ciclosporin than in those treated with tacrolimus. Rates of hypertension and/or the need for hypertensive therapy were either more frequent in ciclosporin groups compared to tacrolimus or equivalent.

Other adverse events that were more evident in ciclosporin-treated patients included gum hyperplasia and, in one trial, hirsuitism, whereas tremor and anaemia were more evident in tacrolimus-treated patients. Infection rates and malignancies were not statistically significantly different between tacrolimus and ciclosporin groups in any of the trials.

Death was the primary reason for discontinuation in the largest study involving combination with azathioprine, with 11 deaths in the tacrolimus group (7.0% of patients) and 16 in the ciclosporin group (10%).

In the largest of the studies involving combination with MMF, the primary reason for study discontinuation in each treatment group was treatment-emergent adverse events, primarily refractory rejection in the ciclosporin group (11%) and neurotoxicity in the tacrolimus group (3.7%). Deaths occurred in 5 patients in the tacrolimus/MMF group (4.6%) and 12 patients in the ciclosporin/MMF group (10%).

Summary of clinical effectiveness issues

The regimens used in individual studies varied widely, but common features are as described below. Unless otherwise stated, regimens were started post-operatively.

Tacrolimus was administered at an initial oral or intravenous dose which varied between studies but was adjusted to achieve defined trough blood levels which also varied but were within the range 10-25ng/ml for an initial period of 1-6 months and 10-20ng/ml thereafter. Similarly, ciclosporin dosing was adjusted to achieve trough levels of 200-600ng/ml during the initial period and 100-300ng/ml thereafter. Corticosteroid regimens also varied, but most study reports specified an initial dose which was tapered and could be discontinued after about 6 months.

The initial dose of MMF, where used, was within the range 2-4 mg/kg and in two studies this was adjusted to achieve trough plasma levels of its metabolite within the range 3-5ng/ml.

Azathioprine was initiated according to local practice and/or at doses within the range 2-4 mg/kg/day; dosing was adjusted to maintain targets for white blood cell counts, though actual targets varied between studies.

No data have been presented on paediatric use.

Summary of comparative health economic evidence

A cost utility analysis was submitted using a Markov model to compare tacrolimus in combination with MMF and corticosteroids compared to standard practice, specified as ciclosporin in combination with MMF and corticosteroids (CsA). Patient level efficacy data from one published phase III trial comparing these regimens was used to establish the number of weeks over the first 12 months post heart transplant in the health state 'treated acute rejection'. This was estimated to be 1.4 fewer weeks per patient for the tacrolimus regimen. Survival analysis based on UK Heart Transplant data was used to estimate the life years gained for patients who had a rejection-free first 12 months and those who had 1 or more episodes of treated acute rejection. This produced an average 0.67 discounted life years gained (8.1 months per patient) and 0.52 QALYs over the remaining 29 years of the model (assuming the average age for a heart transplant is 50 and maximum life expectancy is to age 80) and an incremental cost per QALY gained of just over £35,000. EQ-5D derived utility estimates for treated acute rejection and age-adjusted rejection-free survival states with and without adverse events used in the model were derived from an internet based survey of ~30 cardiothoracic surgeons/specialist nurses. The utilities derived from this exercise did not appear to be particularly robust. .

The base case cost per QALY only included utilities associated with treated acute rejection and rejection free health states but excluded disutilities associated with adverse events. However, the sensitivity analysis was comprehensive and included AE disutilities. In this analysis, the AE that had most impact on the results was the risk of new onset diabetes. As this occurred more frequently in the tacrolimus regimen, inclusion of disutility estimates for new onset diabetes in sensitivity analysis resulted in a much worse incremental cost-effectiveness ratio for tacrolimus. Varying the utility associated with rejection free survival and assuming no overall survival gain increased the incremental cost per QALY gained for the tacrolimus regimen. There were only a few circumstances in the sensitivity analyses in which cost-effectiveness fell below £30,000 per QALY.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: previous SMC advice

Following a full submission the Scottish Medicines Consortium advised in October 2004 that tacrolimus ointment 0.1% and 0.03% (Protopic ®) was recommended for restricted use within NHS Scotland.

Tacrolimus offers a treatment option for adults with atopic dermatitis intolerant of or unresponsive to conventional treatments, and for children aged 2 years or over who are unresponsive to conventional topical therapies. It is a potent immunosuppressant which can be absorbed systemically following topical application, and there are unresolved concerns about possible adverse effects arising from this. Its use should therefore be considered prior to oral therapy when it is deemed that other appropriate options for topical therapy have been exhausted. Its use should be initiated and supervised by dermatologists within secondary care who have experience of treating atopic dermatitis using immunomodulatory therapy. In order to facilitate future investigation of long-term effects of the use of tacrolimus ointment, it is advised that a register of recipients should be established and maintained.

Additional information: comparators

Ciclosporin in combination with mycophenolate mofetil or azathioprine and corticosteroids

Additional information: costs

Costs are shown below for 1 year's treatment with oral tacrolimus and ciclosporin in heart transplant patients, and for 5-days' starting dose for intravenous administration. Where appropriate, these assume a body weight of 60 kg.

In practice, doses are titrated to the individual patient's requirements after initiation and, in one trial according to the manufacturer, dosing of tacrolimus and ciclosporin peaked at around 7 mg/day and 350 mg/day at 8 and 4 weeks respectively. In addition, each of these agents generally forms part of a complex regimen which will vary between cases. Therefore, although the cost comparisons below reflect these doses and the licensed starting and maintenance doses, they are indicative only.

Oral regimen	Cost for one year's treatment
Tacrolimus (Prograf®) hard capsules 0.075 mg/kg/day*	**£2960**
Tacrolimus (Prograf®) hard capsules 2-7 mg /day**	**£1241-£4692**
Ciclosporin (Neoral®) capsules 2-6 mg/kg/day	£856-£2358
Intravenous regimen	**Cost for 5 days' treatment**
Tacrolimus (Prograf®) infusion 0.01-0.02 mg/kg/day	**£310**
Ciclosporin (Sandimmun®) infusion 10-15mg/kg/day	£111-£167

* when used with antibody induction therapy
** when used in combination with mycophenolate mofetil (or sirolimus) plus corticosteroids

Additional information: budget impact

The drug budget impact of introducing tacrolimus has been estimated by the manufacturer at an annual difference of £900 in year 1 rising to £25,000 by year 5. This assumes 21 heart transplant patients (one patient in year 1, rising to 7 in year 5) would be treated with tacrolimus instead of ciclosporin. In terms of market share, these estimates assumed that 20% of eligible patients would be treated with tacrolimus in year one, rising to 100% by year five.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 12 December 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Kobashigawa JA, Miller LW, Russell SD, Ewald GA, Zucker MJ, Goldberg LR, et al. Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. Am J Transplant 2006;6:1377-86.

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Mehra MR, Uber PA, Scott RL, Park MH. Ethnic disparity in clinical outcome after heart transplantation is abrogated using tacrolimus and mycophenolate mofetil-based immunosuppression. Transplantation 2002;74:1568-73.

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Meiser BM, Uberfuhr P, Fuchs A, Schmidt D, Pfeiffer M, Paulus D, et al. Single-center randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of acute myocardial rejection. J Heart Lung Transplant 1998;17:782-8.

Taylor DO, Barr ML, Radovancevic B, Renlund DG, Mentzer RM, Jr., Smart FW, et al. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. J Heart Lung Transplant 1999;18:336-45.

Grimm M, Rinaldi M, Yonan NA, Arpesella G, Arizon Del Prado JM, Pulpon LA, et al. Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients--a large European trial. Am J Transplant 2006;6:1387-97.

Kobashigawa JA, Patel J, Furukawa H, Moriguchi JD, Yeatman L, Takemoto S, et al. Five-year results of a randomized, single-center study of tacrolimus vs microemulsion cyclosporine in heart transplant patients. J Heart Lung Transplant 2006;25:434-9.