Tacrolimus versus cyclosporin in renal transplantation in Italy: cost-minimisation and cost-effectiveness analyses
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of tacrolimus and a cyclosporin-based microemulsion (ME) to prevent graft rejection after kidney transplantation. Both drugs were part of a triple immunosuppressive regimen with azathioprine and corticosteroids.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 to 60 years, with end-stage renal disease, who were suitable candidates for primary kidney transplantation or re-transplantation. The exclusion criteria included prior organ transplant (other than renal) or immune-mediated renal graft failure within the previous year, a high risk of allograft rejection (panel reactive antibody grade 50% or more on the latest sample) and the need for immunosuppressive therapy for concomitant disorders. Patients were also excluded if they had HIV infection, significant hepatic or gastrointestinal disorder, current infection, or evidence or history of malignant disease.

Setting
The setting was secondary care. The economic study was carried out in Milan, Italy.

Dates to which data relate
The dates to which the resource use and effectiveness data related were not reported. The price year was 2000.

Source of effectiveness data
The effectiveness evidence came from a single study, whose details were published elsewhere (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was performed retrospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were carried out in the preliminary phase of the group. These assumed that the rate of acute rejection in tacrolimus-treated patients during the first 6 months after transplantation would be 25%. A total of 450 patients were required for 80% power (significance level 0.05) to detect a difference of 13% in the rate of acute
rejection. The method of sample selection was not reported. A sample of 560 patients was enrolled into the study. There were 287 in the tacrolimus group, of which 200 were men, and 273 in the cyclosporin ME group, of which 171 were men. In the tacrolimus group, the mean age was 42.4 (+/- 10.4) years for the patients and 42.0 (+/- 14.7) years for the donors. In the cyclosporin ME group, the mean age was 43.8 (+/- 10.4) years for the patients and 42.9 (+/- 14.1) years for the donors. One patient in the tacrolimus group and two patients in the cyclosporin ME group did not receive the treatment.

Study design
This was a prospective, randomised parallel-group trial, which was carried out in 50 centres in seven European countries (Austria, Belgium, Germany, Italy, Luxembourg, Spain and Switzerland). The patients were randomised on a one-to-one ratio and the unit of randomisation was the patient. Follow-up assessments were scheduled on days 1, 7, 14 and 21 and at 1, 3 and 6 months. The loss to follow-up was 42 patients in the tacrolimus group and 80 patients in the cyclosporin ME group. The assessment was not blind and both the clinicians and the patients were aware of the randomised allocation.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis, although three patients were excluded from this analysis because they did not receive a study drug or did not undergo transplantation. Several health outcomes were used in the primary study. Those relevant to the present analysis were the rates of acute rejections (based on clinical signs and symptoms), steroid-sensitive acute rejections, steroid-resistant acute rejections (those rejections which did not resolve after corticosteroid bolus therapy), deaths, graft losses, and patient and graft survival. The two study groups were well balanced at baseline with respect to their demographic and clinical characteristics.

Effectiveness results
The average rates of acute rejection were 32.5% in the tacrolimus group and 51.3% in the cyclosporin group (difference: 18.8%, 95% confidence interval, CI: 10.7 - 26.8; p<0.001).

The rates of steroid-sensitive acute rejection were 23.8% (tacrolimus) and 31% (cyclosporin), respectively, (difference 7.2%, 95% CI: -0.2 - 14.6; p=0.056).

The rates of steroid-resistant acute rejection were 10.5% (tacrolimus) and 24.4% (cyclosporin), respectively, (difference: 13.9%, 95% CI: 7.6 - 20.1; p<0.001).

The rates of death were 0.7% (tacrolimus) and 1.5% (cyclosporin), respectively, (difference: 0.8%, 95% CI: -1 - 2.5; p=0.366).

The rates of graft losses were 5.2% (tacrolimus) and 8.1% (cyclosporin), respectively, (difference: 2.9%, 95% CI: -1.8 - 7.2; p=0.139).

The rates of patient survival at 6 months were 99.3% (tacrolimus) and 98.5% (cyclosporin), respectively, (difference not statistically significant).

The rates of graft survival were 94.8% (tacrolimus) and 91.9% (cyclosporin), respectively, (difference not statistically significant).

Thus, there were 284 surviving patients (out of 286) in the tacrolimus group and 267 (out of 271) in the cyclosporin group. Of these, there were 271 patients with a functioning graft in the tacrolimus group and 249 in the cyclosporin group.

Clinical conclusions
The effectiveness analysis showed that tacrolimus treatment was more effective than cyclosporin ME in reducing the overall rates of acute rejection and steroid-resistant acute rejections. The survival data for patients and grafts were
Measure of benefits used in the economic analysis
The benefit measure used in the economic analysis was the number of surviving patients with a functioning graft. This was derived directly from the effectiveness study. However, a cost-minimisation analysis was also conducted because there was no statistically significant difference in terms of survival between the two study drugs.

Direct costs
Discounting was not relevant because the costs were incurred in less than two years. The unit costs were not reported separately from the quantities of resources used. The health services included in the economic evaluation were immunosuppressive therapy (tacrolimus or cyclosporin ME) and concomitant anti-rejection therapy, hospitalisation (in ordinary ward or intensive care unit), dialysis, and diagnosis of graft rejection. The drugs used to treat adverse events and physician fees were also included. The costs of the transplant and subsequent hospital stay were not considered. The cost/resource boundary adopted was that of the hospital. The drug costs were taken from the Italian Red Book. A discount of approximately 50% was applied to the drug retail price in order to reflect the price conditions in a hospital. The hospitalisation costs were derived from the Ospedale Maggiore, Policlinic of Milan. The remaining costs were derived using the actual reimbursement tariffs in the Lombardy Region. Resource use was estimated using data from the trial and assuming that all the patients were treated in Italy. All the costs were inflated to 2000 values using the Italian Institute for Statistics index for health care-related services and expenditures.

Statistical analysis of costs
Statistical analyses of the costs were conducted to test the statistical significance of the difference in total costs. Depending on the distribution of the data, Student's t-test or chi-squared tests were applied.

Indirect Costs
The indirect costs were not included.

Currency
Euros (Euro).

Sensitivity analysis
One-way sensitivity analyses were performed to assess the robustness of the estimated cost-effectiveness ratios and total costs to variations in the costs of hospitalisation, the study drug and concomitant medication. The lower and upper limits of the CIs (reported in the effectiveness study) for the difference in surviving patients with rejection-free graft were also varied.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The estimated total costs per patient were Euro 11,288 in the tacrolimus group and Euro 13,064 in the cyclosporin ME group. Thus, there was a cost difference of Euro 1,776.

In the cost-minimisation analysis, it was estimated that the cost per surviving patient with a functioning graft was Euro 11,913 with tacrolimus and Euro 14,218 with cyclosporin ME. The difference was Euro 2,305. The cost per surviving patient was Euro 11,368 with tacrolimus and Euro 13,260 with cyclosporin ME, and the difference was Euro 1,892.
The estimated costs were robust to the variations investigated in the sensitivity analysis.

**Synthesis of costs and benefits**
An incremental cost-effectiveness analysis was performed to combine the costs and benefits of the two treatments. However, the cost-effectiveness ratio was not calculated because tacrolimus was the dominant option (higher benefits and lower costs compared with cyclosporin ME).

**Authors’ conclusions**
Compared with the cyclosporin-based microemulsion (ME), tacrolimus was a cost-effective treatment for patients undergoing renal transplants. Although the survival rates were similar between the two study groups, tacrolimus was both more effective (in terms of episodes of acute rejections) and cheaper than cyclosporin ME under a wide range of assumptions in Italy.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparators was clear. The authors stated that both tacrolimus and cyclosporin ME represented two widely used immunosuppressive agents for the prevention of acute-rejection in renal-allograft recipients. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness used a randomised controlled trial, which was carried out in several centres throughout Europe. This ensures the high internal validity of the analysis. Sample size calculations were performed in the preliminary phase of the analysis and the loss to follow-up was reported. The method of randomisation was mentioned, while details on the outcome evaluation were reported in the primary study. The study groups were quite comparable at baseline. These issues tend to increase the internal validity of the analysis. However, the method of sample selection was not stated and the evaluation was not blind.

**Validity of estimate of measure of benefit**
The benefit measure used in the economic analysis was derived from the effectiveness study.

**Validity of estimate of costs**
The perspective adopted in the study was explicitly reported. It appears that all the relevant categories of costs have been included in the analysis. Statistical analyses of the costs were conducted. In addition, the authors carried out several sensitivity analyses on the cost side of the study, in order to evaluate the robustness of the estimated total costs. The time horizon of the study was 6 months and discounting was, therefore, irrelevant. The price year was reported, thus making reflation exercises in other settings feasible. A detailed breakdown of the costs was given. However, the unit costs and the quantities of resources used were not reported separately. These limit the reproducibility of the study results to other settings. The authors identified the main cost drivers of the analysis.

**Other issues**
The authors compared some of their findings with those from studies published in the USA and the UK. They also made some comparison with studies evaluating liver transplantation, due to similarities with the conclusions of the present analysis. The authors did not address the issue of the generalisability of the study results to other settings although some sensitivity analyses were conducted. The focus of the analysis was on the economic implications of the treatments under study and this was consistently reported in the conclusions of the analysis.

**Implications of the study**
The study results suggested that tacrolimus was associated with a more convenient economic profile from the
perspective of the Italian hospitals, and thus should be recommended for the prevention of graft rejection after kidney transplantation.

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Other publications of related interest

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