A cost-effectiveness analysis of tacrolimus versus cyclosporine microemulsion following kidney transplantation
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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
Two treatment for preventing acute graft rejection and improving graft survival after kidney transplantation were investigated. These were tacrolimus (0.3 mg/kg daily) and cyclosporine microemulsion (CyA-ME; 8 to 10 mg/kg daily).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients with end-stage renal disease suitable for primary or repeated renal transplantation. Patients were excluded from the study if they were pregnant or nursing, or if they had a recently measured PRA grade of greater than 50%. They were also excluded if they were allergic or intolerant to antimetabolites, HCO-60, steroids, macrolide antibiotics, tacrolimus, cyclosporine, or related compounds. Further exclusion criteria were a positive HIV status of the donor or recipient, the patient had already received an organ other than a kidney, or if there was a pre-existing malignancy or pre-existing uncontrolled systemic infection. Female patients of childbearing age had to maintain an effective birth-control practice throughout the duration of the study.

Setting
The setting was a hospital. The effectiveness study was carried out in 50 centres in Europe (Austria, Belgium, Germany, Italy, Luxembourg, Spain and Switzerland). However, the economic study referred to only three centres, which were Germany, Italy and Spain.

Dates to which data relate
No dates were given. No price year was reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study, whose main results were published elsewhere (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was carried out on a different patient population from that used in the effectiveness analysis.

Study sample
Power calculations to determine the sample size were not performed. The method used to select the sample was not reported. A sample of 557 patients who underwent kidney transplantation was included in the analysis. Of these, 286 patients were administered tacrolimus and 271 CyA-ME. The mean age of the patients in the tacrolimus group was 42.4 years, and 69.9% were men. The mean age of the patients in the CyA-ME group was 42.8 years, and 63.1% were men.

**Study design**

This was a retrospective, open-label, randomised parallel-group trial, which was carried out in 50 centres in Europe. The method of randomisation was not provided. All of the patients also received additional immunosuppressive therapy involving corticosteroids (tapered from 20 mg/day at day 2 to 5 mg/day at day 43) and azathioprine (1 to 2 mg/kg per day). The length of follow-up was 6 months, and data were available for 244 patients (85.3%) in the tacrolimus group and 189 patients (69.7%) in the CyA-ME group. The loss to follow-up was mainly due to withdrawal caused by adverse events and graft loss.

**Analysis of effectiveness**

The basis of the analysis of effectiveness was intention to treat. The primary health outcomes assessed were estimates of patient survival and graft survival (both derived using the Kaplan-Meier approach) and the incidence of acute rejection. Secondary outcomes, such as creatinine levels and occurrence of dialysis and adverse events, were also assessed. The study groups were comparable at baseline in terms of their demographics, clinical condition and donor characteristics.

**Effectiveness results**

At 6 months, patient survival was 99.3% in the tacrolimus group and 98.5% in the CyA-ME group. Graft survival was 94.6% in the tacrolimus group and 91.9% in the CyA-ME group. None of the differences achieved statistical significance.

The incidence of acute rejection was 19.6% in the tacrolimus group and 37.3% in the CyA-ME group, (p<0.001).

The analysis of the adverse events showed that the safety profiles of the two treatments were comparable.

**Clinical conclusions**

The authors concluded that the tacrolimus-based treatment was more effective than CyA-ME in reducing the incidence of graft rejection. The treatments were similar in terms of patient survival.

**Measure of benefits used in the economic analysis**

The benefit measures used in the economic analysis were patient and graft survival and rejection-free graft rates. These were derived directly from the effectiveness analysis.

**Direct costs**

Discounting was irrelevant as the time horizon of the study was 6 months. The unit costs and the quantities of resources were not reported. The health service costs included in the economic evaluation were for the study drugs, concomitant medications, hospitalisation, dialysis, and the treatment of rejection episodes. The cost/resource boundary was that of the healthcare provider. The cost data were originally derived from 50 centres in Austria, Belgium, Germany, Italy, Luxembourg, Spain and Switzerland, but only data from Italy, Germany and Spain were used in the analysis. The resources used were estimated using actual data from the clinical trial. The price year was not reported.

**Statistical analysis of costs**

No statistical analysis of the costs was carried out.
Indirect Costs
The indirect costs were not included in the analysis.

Currency
Euros.

Sensitivity analysis
Sensitivity analyses were conducted to assess the robustness of the estimated cost-effectiveness ratios. These were only carried out on cost drivers (hospitalisation, study drugs and concomitant medication). The type of analysis was not reported.

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

Cost results
The total costs of the interventions were not reported. The authors stated that "Italy had the highest difference in costs per patient (1,776 euros) followed by Germany (1,075 euros), and Spain (524 euros)". It was also reported that the hospitalisation costs, incidence of dialysis and costs for graft rejection were lower in the group of patients receiving tacrolimus than in the CyA-ME group.

Synthesis of costs and benefits
The costs and benefits were combined using an average cost-effectiveness analysis.

For treatment with tacrolimus, the cost per surviving patient was 11,386 euros in Italy, 11,667 euros in Germany, and 6,436 euros in Spain. For treatment with CyA-ME, the corresponding cost were 13,260 euros in Italy, 12,851 euros in Germany, and 7,019 euros in Spain.

For treatment with tacrolimus, the cost per surviving graft was 11,913 euros in Italy, 12,227 euros in Germany, and 6,745 euros in Spain. For treatment with CyA-ME, the corresponding costs were 14,218 euros in Italy, 13,780 euros in Germany, and 7,526 euros in Spain.

For treatment with tacrolimus, the cost per rejection-free graft was 16,902 euros in Italy, 17,348 euros in Germany, and 9,570 euros in Spain. For treatment with CyA-ME, the corresponding costs were 26,821 euros in Italy, 25,994 euros in Germany, and 14,197 euros in Spain.

The estimated cost-effectiveness ratios were unaffected by the variations examined in the sensitivity analyses.

Authors’ conclusions
Compared with patients administered cyclosporine microemulsion (CyA-ME), patients treated with tacrolimus had only minor incidences of acute rejection and used fewer resources in the 6 months following kidney transplantation. Consequently, although the drug acquisition costs were higher, tacrolimus proved to be the dominant treatment (more effective and less costly) over CyA-ME.

CRD COMMENTARY - Selection of comparators
The authors did not justify the choice of the interventions compared in the analysis. The authors stated that the two drugs had been compared in several published studies. You should assess whether the drugs represent widely used treatments in your own setting.
Validity of estimate of measure of effectiveness
The analysis of effectiveness used a randomised controlled clinical trial, which was appropriate for the study question. It was carried out in several centres in Europe, and consequently the internal validity of the analysis appears to have been high. However, the randomisation process and sample selection method were not reported. The study sample seems to have been representative of the study population. In addition, the basis for the analysis of the clinical study was intention to treat. The study groups were comparable at baseline. These issues tend to enhance the internal validity of the analysis. However, it has to be noted that power calculations were not performed, although the sample size was quite large.

Validity of estimate of measure of benefit
The benefit measures used in the economic analysis were derived directly from the effectiveness study (see comments in the previous field).

Validity of estimate of costs
The costs were analysed from the perspective of the healthcare provider, and it appears that all the relevant categories of costs have been included. However, the cost analysis presents some limitations. The unit costs and the quantities of resources were not reported separately. The price year was not given, thus hindering reflation exercises to other settings. The total costs were not reported, with only the differences in the costs being provided. The costs and quantities were treated deterministically in the base-case. Sensitivity analyses were performed, but there were no details of the ranges over which the cost data were varied. Also, the type of analysis conducted was unspecified.

Other issues
The authors did not compare their findings with those from other studies. Also, the issue of the generalisability of the study results to other settings was not addressed. Limited sensitivity analyses were performed on the cost data, but the unit costs were not reported. Consequently, the external validity of the analysis is somewhat limited. The authors appear to have presented their results selectively.

Implications of the study
The authors suggest that treatment with tacrolimus should be adopted for patients undergoing kidney transplantation.

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None stated.

Bibliographic details

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12176519

Other publications of related interest
Sperschneider H. A large, multicentre trial to compare the efficacy and safety of tacrolimus with cyclosporine microemulsion following renal transplantation. Transplantation Proceedings 2001;33:1279-81.

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MeSH
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