Cyclosporine minimization and cost reduction in renal transplant recipients receiving a C2-monitored, cyclosporine-based quadruple immunosuppressive regimen


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 present study compared a C2-monitored cyclosporine-based quadruple immunosuppressive regimen based on target 2-hour postdose cyclosporine with a strategy monitored by means of trough (C0) levels in de novo kidney transplant recipients. Patients received thymoglobulin (1.5 mg/kg/day intravenously) as induction, followed by triple immunosuppression with azathioprine (5 mg/kg per day orally for 3 days and 2.5 mg/kg per day thereafter) or mycophenolate mofetil (500 to 1,000 mg orally twice daily), prednisone (1 mg/kg per day orally for 3 months and 0.1 mg/kg per day thereafter), and cyclosporine monitored by C2 or C0 concentration.

Cyclosporine was tapered to maintain the C2 level between 1,000 and 1,200 ng/mL during months 0 to 3, and between 600 and 1,000 ng/mL thereafter; and C0 level between 250 and 350 ng/mL during months 0 to 3, and between 100 and 250 ng/mL thereafter.

Type of intervention
Rehabilitation and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
All adult renal transplant recipients at a university hospital were considered for enrolment. Patients were excluded if they had a known allergy to cyclosporine, or documentation of malignancy within 2 years (with the exception of skin malignancies). Pregnant women or nursing mothers, women of childbearing potential who were not practising a reliable form of birth control, and patients with active infection were also excluded.

Setting
The setting was tertiary care. The economic study was carried out in Missouri, USA.

Dates to which data relate
The effectiveness evidence and resource used data were collected from March 2001 to March 2003. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness analysis.
**Study sample**
The sample size and power calculations were reported. A sample size of 43 patients in each arm was needed to give a power of 80% for detecting a 25% difference in acute rejection with a significance level of 5%. The method of sample selection was stated to be sequential. Fifty patients were enrolled in each sequential cohort, the majority of which were men (70% in the C2 group and 62% in the C0 group). The mean average age was 51 (±/− 12) years in the C2 group and 43 (±/− 14) years in the C0 group.

**Study design**
This was a prospective, sequentially designed, cohort trial that was conducted in a single centre. The follow-up period was 6 months after transplant. No loss to follow-up was reported. Blinded assessment was not reported.

**Analysis of effectiveness**
The primary end point of the study was the rate of acute rejection at 6 months. The secondary end points were allograft function, infection and adverse events. The analysis of the clinical study was conducted on an intention to treat basis. Univariate analyses were performed, using Student’s t-test for continuous variables and the chi-squared test for categorical variables. All statistical tests were two-tailed. The patients in the C2 group tended to be older, (p=0.08), but were similar in other baseline characteristics (e.g. white origin, gender, type of donor).

**Effectiveness results**
Patient and graft survivals were 100% in both groups at 6 months.

The incidence (4% versus 6%; p non significant) and severity of acute rejection were similar between the two groups. One patient in the C2 arm and two patients in the C0 arm demonstrated a Banff Grade IB, steroid-sensitive rejection 3 months after transplant. One patient in the C2 arm demonstrated a Grade IIB rejection 14 days after transplantation, while one in the C0 arm demonstrated a Grade IIA rejection 7 days after transplantation. The mean serum creatinine at 6 months after transplantation was 1.5 (+/− 0.5) mg/dL in the C2 arm, and 1.5 (+/− 0.6 mg/dL) in the C0 arm, (p non significant).

The mean blood pressures in both groups improved after transplantation. There were no serious fungal or viral infections, including cytomegalovirus, during the study period. The incidence of bacterial infections was similar between the groups. There were no occurrences of malignancy. Post-transplant diabetes mellitus occurred in one patient in each arm.

Lower cyclosporine doses were achieved in the C2 arm than in C0 arm by one month after transplantation, and these were sustained throughout the 6-month study period. At one month, the mean cyclosporine dose was 390 (+/− 116) mg/day in the C2 arm versus the 453 (+/− 161) mg/day in the C0 arm, (p<0.05). A similar trend continued at 6 months with average doses of 199 (+/− 73) mg/day in the C2 arm versus 273 (+/− 104) mg/day in the C0 arm, (p<0.001).

The C2 levels were lower than international guidelines throughout the study period. More specifically, 33% lower at one month, 38% lower at 3 months, and 48% lower at 6 months.

**Clinical conclusions**
According to the authors, the major finding of the study was that a quadruple immunosuppressive regimen with cyclosporine monitored by C2 concentrations, which were lower than internationally recommended guidelines, prevented acute rejection and minimised toxicity. Patient and graft survival were excellent in this 6-month trial. Allograft function was also excellent, with low acute rejection rates and low serum creatinine values. Although the follow-up was brief, it is possible that lower C2 concentrations might decrease the risk of long-term complications such as infection or malignancy.
Measure of benefits used in the economic analysis
As the clinical results were similar between the groups, the authors reported cost-differences. The paper was, in effect, a cost-minimisation analysis.

Direct costs
The only direct costs included in the study were those of immunosuppressive medications and other medications. Drug costs were calculated with the exclusion of antibody agents, antiviral therapy for prophylaxis and short-term antibiotic treatments, although the use of these agents was similar between the groups. The medication costs were based on the average wholesale price. The costs and the quantities were estimated from actual data. The 12-month medication cost was calculated from the actual cost of immunosuppression and concomitant medications during months 0 to 6 after transplant plus the expected costs during months 6 to 12, postoperatively determined from the 6-month medication cost. Discounting was not carried out since the costs were incurred during less than two years. The quantities and the costs were not analysed separately. The price year was 2003.

Statistical analysis of costs
The costs were treated stochastically. Univariate analyses were performed, using Student's t-test for continuous variables and the chi-squared test for categorical variables. All statistical tests were two-tailed.

Indirect Costs
No indirect costs were reported.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analysis was reported.

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

Cost results
During the first 6 months, cyclosporine monitored by C2 concentrations was less expensive than cyclosporine monitored by C0. The costs of cyclosporine were $2,811 (+/- 933) in the C2 arm versus $3,584 (+/- 1,363) in the C0 arm, (p=0.001).

The total 6-month immunosuppression costs were lower in the C2 arm than in the C0 arm, $3,981 (+/- 1,123) versus $4,809 (+/- 1,575), (p=0.003). This translated into average cost-savings for C2-monitored patients of $773 in cyclosporine costs, (p<0.001), and $828 in total immunosuppressive costs, (p<0.001).

At 6 months, the cumulative immunosuppressive and concomitant medication costs were lower in the C2 arm than in the C0 arm, $7,551 (+/- 3,639) versus $8,111 (+/- 3,898), but were not statistically significant.

The estimated 12-month cost and use of concomitant medications was not statistically different, $13,457 (+/- 8,634) in the C2 group versus $14,462 (+/- 7,233) in the C0 group.

Synthesis of costs and benefits
Not relevant.
Authors' conclusions
The study demonstrated the safety and efficacy of lower than previously described 2-hour postdose cyclosporine (C2) target concentrations using thymoglobulin induction therapy in renal transplant recipients. Further, there may be pharmacoeconomic benefits of C2 monitoring.

CRD COMMENTARY - Selection of comparators
The choice of the comparator was explicitly justified on the basis that it was a usual and current practice in the authors' setting. You should judge whether these drug regimens are relevant in your own setting, or whether other comparators from other treatment or drug classes could also have been relevant.

Validity of estimate of measure of effectiveness
The analysis was based on a cohort trial, with all the inherent potential problems associated with using non-randomised designs to derive comparative measures of effectiveness between treatments. No blinding methods were reported, which might also have introduced some bias. On the other hand, the use of power calculations to determine the sample size and an analysis based on intention to treat represent significant strengths. It seems likely that the study sample was representative of the study population and the comparability of the study groups was reasonable. Univariate statistical analyses were performed, but no sensitivity analysis was performed to explore uncertainty.

Validity of estimate of measure of benefit
Since the clinical outcomes were shown to be similar between strategies, the study was therefore classified as a cost-minimisation analysis.

Validity of estimate of costs
There was insufficient detail of the quantities and resource used for the cost estimation. Although it was not stated, some relevant costs could have been omitted from the analysis since the only costs considered were those of medications, and this might have affected the authors' conclusions. The costs and the quantities were not reported separately, thus the analysis could not be easily extrapolated to other settings. The sources of the cost data were not fully reported. All these factors could affect the robustness of the cost results. The statistical analysis of the costs was not reported separately. Discounting was not necessary since all the costs were incurred during less than two years. The price year was reported, which will help any future reflation exercises.

Other issues
The authors compared their findings with those from other relevant studies, but found their results were different. The generalisability of the results to other settings was not addressed. The authors do not appear to have presented their results selectively and the scope of the analysis was clearly reflected in their conclusions. In addition to the non-randomised study design (mentioned already), the authors acknowledged some further limitations of their study. For example, the fact that the majority of patients in the study were at relatively low risk for acute rejection. Also, because the follow-up period was brief, the long-term effects of C2 monitoring were not defined.

Implications of the study
The data indicated potential policies for the management of cyclosporine with thymoglobulin induction therapy to maximise efficacy, minimise toxicity, and reduce drug costs. Further study of C2 versus C0 monitoring is needed to compare the long-term effects on allograft survival and renal function. C2 concentrations in populations at greater risk of rejection should also be studied further.

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