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ORIGINAL ARTICLE

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Economic evaluation of everolimus versus mycophenolate mofetil in combination with cyclosporine and prednisolone in de novo renal transplant recipients

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Abstract An economic evaluation was undertaken alongside a multicentre, international, trial of everolimus (Certican). Resource usage within the trial was assessed, and the cost implications of the use of everolimus were evaluated. Recipients of a primary cadaveric kidney transplant were recruited into a double-blind trial and received either everolimus 1.5 mg ($n = 194$); everolimus 3 mg ($n = 198$) or mycophenolate mofetil (MMF) 2 g ($n = 196$). Clinical outcomes and resource usage were monitored for 12 months following transplantation. Local costs were obtained, and global analysis using health sector PPP rates was undertaken. The mean overall cost of treatment was $33,715 (95%CI $30,013–$37,417) with everolimus 1.5 mg, $38,519 (95%CI $34,094–$42,943) with everolimus 3 mg and $36,509 (95%CI $32,430–$40,587) with MMF. Differences between the three groups did not reach statistical significance. In conclusion, the economic analysis showed statistical equivalence over the three arms of the trial. Further work is required to demonstrate the cost consequences of the use of everolimus compared with MMF in renal transplantation patients.

Keywords Everolimus · Certican · Mycophenolate mofetil · Pharmacoeconomic

Introduction

Despite a marked reduction in acute rejection rates in recent years [1], chronic rejection continues to exert a heavy toll in terms of long-term renal graft loss. As the therapeutic armamentarium expands and immunosuppressive strategies are refined, the new goal is to maintain low levels of acute rejection whilst also addressing the need to protect the graft against contributory factors for chronic rejection and late graft loss. However, prevention of chronic rejection is a complex challenge, requiring minimization of graft injury from both immune and non-immune mechanisms [2]. Risk factors include the number and severity of acute rejection episodes, vascular remodelling of the graft and intimal thickening, occurrence of cytomegalovirus (CMV) infection, drug-induced toxicity (most notably nephrotoxicity associated with use of calcineurin inhibitors) and certain co-morbid disease conditions [3].

Everolimus (Certican, Novartis Pharma AG, Basel, Switzerland) is a novel proliferation inhibitor that has been shown in preclinical models [4, 5], and more recently in clinical trials [6, 7], to target risk factors for chronic rejection. It works synergistically with cyclosporine (CsA) allowing for CsA dose reduction without compromising acute rejection prophylaxis. Everolimus has been shown to reduce CMV infection rates, in comparison with mycophenolate mofetil (MMF) [7] and azathioprine [6], and to inhibit vascular remodelling in heart transplant recipients [8]. Further clinical trials are currently underway to evaluate the clinical impact of

these characteristics when everolimus is used in combination with reduced-dose CsA.

If the attributes of everolimus translate to significant clinical benefits, inclusion of everolimus within a triple-therapy regimen could be expected to reduce the resource utilization of medical care, both in terms of management of adverse clinical events and, ultimately, through a reduced need for dialysis or re-transplantation following graft loss. We undertook an economic evaluation alongside a 12-month multicentre, international phase III trial of everolimus versus mycophenolate mofetil in combination with CsA microemulsion and prednisolone in de novo renal transplant patients. The objective of our analysis was to compare the resource usage and costs associated with each immunosuppressive regimen over the first 12 months post-transplantation.

Methods

Study design

The study was a prospective, double-blind, placebo-controlled trial of 588 adult patients undergoing their first kidney transplant, undertaken in fourteen countries. Patients were randomly allocated to one of three treatment groups: everolimus 1.5 mg; everolimus 3 mg; MMF 2 g (CellCept, Roche Pharmaceuticals, Basel, Switzerland). The first dose of study medication was given within 48 h of surgery, after which medication was given twice daily. All patients received CsA microemulsion (Neoral, Novartis AG, Basel, Switzerland) and prednisolone. Patients with suspected acute rejection underwent renal biopsy and were treated with additional immunosuppressive agents as required.

The primary clinical outcome measures were a composite efficacy endpoint of biopsy-proven acute rejection, graft loss, death and loss to follow-up at 6 months, and graft loss, death or loss to follow-up at 12 months. Among the secondary endpoints was the effect on the use of health system resources during the first 12 months after transplantation. The primary outcome for the economic evaluation was the mean treatment cost per patient in each group at 12 months post-transplantation.

The study was performed in accordance with the ethical standards required by the Declaration of Helsinki, the European Community Directive 91/507/EEC and the US 21 code of Federal Regulations. All persons gave their informed consent prior to their inclusion in the study.

Cost analysis

The study did not attempt to capture all of the costs of transplantation. Costs included were only those that might be expected to vary according to immunosuppressive therapy. For the purpose of data collection and economic analysis, the perspective of the hospital was adopted. Total estimated costs per patient were calculated by estimation of the cost of hospitalization, diagnostic procedures (biopsies, ultrasounds or other visualization techniques), laboratory tests, outpatient or emergency room visits, post-operative dialysis, immunosuppressive therapy or major use of concomitant medication.

The cost of everolimus was unavailable at the time of analysis, and, therefore, the cost of MMF was excluded in order for an impartial comparison of costs to be made. For all other immunosuppressive drugs, the unit cost was the cost per milligramme for the drug. The total cost per drug for each patient was calculated from the average daily dose multiplied by the unit cost. For the purposes of the economic analysis the top 12 concomitant medications (ranked by patient usage and days of usage) were identified. No dosing information was available for concomitant medication, so the total cost for concomitant medications for each drug for each patient was calculated from the number of days the patient received therapy multiplied by the recommended average daily dose, multiplied by the cost per unit.

Dialysis costs were calculated by multiplication of the proportion of the year spent on dialysis by annual unit dialysis costs. If the patient had a graft failure, then the number of days on dialysis was calculated from the date of graft loss to the 12-month post-transplantation date. The same approach was used for patients with graft loss who did not have a kidney re-transplantation, since the availability of an organ for a second transplant was not affected by the original immunosuppressive regimen.

Twenty-one patients had a graft loss with no record of post-transplantation dialysis. Those patients were assumed to have required dialysis, with duration estimated as the days between the graft loss and either the day of death or 365 days after the date of transplantation. For the four patients who underwent re-transplantation, dialysis was assumed from the date of graft loss until either the day of death or 365 days after the date of transplantation.

All resources were valued at 1999 prices. Discounting was not employed, since costs and benefits are estimated for a 12-month study period only. Unit costs were obtained or estimated for each item of resource used in each country in order for a cost vector in local currency to be obtained. Local currency unit costs were converted to US dollar costs by means of a purchasing power parity (PPP) rate, since that more closely reflects true purchasing differences in the health sectors of the countries concerned than standard exchange rates. Hence, in countries where the relative cost of, for

example, nurse wages, are much higher, the difference is accounted for by the use of PPPs. The country-specific vectors of unit costs were applied to the quantities of resources used by each patient so that the cost of treatment could be calculated in PPP $US, which was then used for the calculation of average cost per treatment group. Where no country-specific unit costs were available (Russia, Czech Republic and South Africa) the median unit costs in PPP $US from the other countries was used instead.

Pooling of data

The validity of the use of pooled resource utilization data from all countries was tested statistically. Overall resource use (drug therapy, diagnostic procedures, laboratory tests, etc.) was expected to relate proportionately to length of stay in hospital. Therefore, statistical testing for interaction between treatment and country was undertaken for total length of hospital stay instead of for individual categories of resource use. The total number of days in hospital over the 12-month period was taken as the dependent variable, and the treatment group and country as predictor or explanatory variables [9].

From the use of this approach, there was no statistical evidence that between-country differences influenced the effect of treatment on length of initial stay (ANOVA model) or requirement for follow-up hospitalization (chi-squared test). Similarly, logistic regression modelling showed that the effect of treatment on the incidence of biopsy-confirmed episodes of acute rejection did not differ between countries, although the incidence of biopsy-confirmed acute rejection did vary by country.

When an ANOVA model was applied to cost analysis data, with total treatment cost as the dependent variable and the drug and country as predictor or explanatory variables, there was again no statistical evidence of an interaction between the group and country, and, thus, the effect of treatment on total cost did not differ between countries, despite local variations in treatment costs.

In the absence of statistical evidence suggesting that treatment-related differences are affected by country, there was no justification for data to be reported by individual country, and, therefore, pooled resource data from all participating countries have been used throughout.

Patient population

In total, 588 patients were eligible for intention-to-treat analysis. One hundred and ninety-four were randomly allocated to receive everolimus 1.5 mg, 198 to everolimus 3 mg and 196 to MMF 2 g. Patients' demographic details and baseline characteristics are shown in Table 1. The populations were well balanced in terms of race, age, height and weight across the treatment arms, and there were no significant differences between treatment groups in terms of demographic, clinical or laboratory parameters. Three hundred and eighty-one patients completed the 12-month study.

Table 1 Patients' demographic and baseline characteristics. *P* values from one-way ANOVA were all non-significant

Characteristic	Everolimus 1.5 mg ($n=194$)	Everolimus 3 mg ($n=198$)	MMF 2 g ($n=196$)
Male (% patients)	58.8	64.1	70.9
Race (% patients)			
Caucasian	93.3	89.4	87.2
Black	2.1	4.5	5.6
Oriental	2.1	2.5	3.1
Other	2.6	3.5	4.1
Mean age (years)	45.2	44.1	46.1
Mean height (cm)	169.0	170.7	170.8
Mean weight (kg)	70.4	70.9	71.2
Mean blood pressure (mmHg)			
Diastolic	84.7	84.9	85.1
Systolic	146.0	143.7	144.2

Statistical analysis

All statistical analyses were performed on the intention-to-treat (ITT) population. All statistical tests were interpreted at a significance level of 0.05. All *P* values reported are for two-sided alternative hypotheses.

Between-group analysis was performed by use of a one-way ANOVA test for continuous variables (e.g. daily dose of therapy). If the one-way ANOVA (to compare the mean outcomes across the three groups) resulted in a significant *P* value (<0.05) when mean outcomes across the three groups were compared, then multiple pairwise comparisons (i.e. group 1 versus group 2, group 2 versus group 3, and group 1 versus group 3) were undertaken by means of two independent sample *t* -tests to identify where the between-group differences lay. Bonferroni-corrected *P* values were reported from the pairwise comparisons [10].

For categorical variables (e.g. use of drug), between-group analyses were performed by use of the Pearson chi-squared test. For dichotomous categorical variables, between-group comparisons were made via a chi-squared test. If the overall chi-squared test resulted in a significant *P* value (<0.05), then multiple pairwise chi-squared *t* -tests were undertaken in the same way as for the continuous variable analysis.

Results

Clinical end-points

There were no statistically significant differences between the treatment groups in terms of the primary composite end-points of efficacy failure at 6 or 12 months (Table 2). Neither were there any significant between-group differences in any of the individual efficacy measures at either 6 or 12 months, or the incidence of biopsy-confirmed episodes of acute rejection. At 12 months, the incidence of graft loss was 4.6% in the everolimus 1.5 mg group, 10.6% with everolimus 3 mg and 9.2% with MMF (not significant).

Resource use

The three treatment cohorts required a similar level of resource in terms of hospitalization, diagnostic procedures, laboratory tests and outpatient consultations. A smaller proportion of patients in the everolimus 1.5mg group required dialysis than in either of the other two treatment groups (21.6% compared with 27.3% in the everolimus 3 mg group and 26.5% in the MMF group). The mean duration of dialysis per patient in each cohort was 16.5 days, 37.3 days and 31 days, respectively. These differences were not statistically significant.

Use of additional immunosuppressive drugs other than as specified by protocol was also comparable between the three treatment groups, including administration of steroids and MMF other than by protocol. Total cumulative CsA dose over the 12-month study period was significantly lower in the everolimus 3 mg group than in the MMF group (68,424 mg compared with 83,450 mg, $P=0.002$) (Table 3).

There were no significant differences in mean duration or dose of concomitant medications between the treatment arms, including omeprazole, nifedipine, atenolol, amphotericin B, CMV treatment or lipid-lowering therapy (Table 3).

Resource cost

There were no statistically significant differences in the mean cost of any resources except for the cost of CsA therapy (Table 4). The average cost of CsA was $4,454 and $4,124 in the everolimus 1.5 mg and 3 mg groups, respectively, and $5,163 among patients receiving MMF. The mean difference between everolimus 1.5mg and MMF was −$709 (95% CI −$1,404 to −$14, $P=0.04$) and −$1,038 between everolimus 3 mg and MMF (95% CI −$1,730 to −$347, $P=0.001$).

The average cost of post-transplantation dialysis treatment was $3,495 (95% CI $1,424–$5,565) in the everolimus 1.5 mg group, $7,459 (95% CI $4,492–$10,426) in the everolimus 3 mg group and $6,304 (95% CI $3,469–$9,139) in the MMF cohort. These differences were predominantly due to variations in duration of dialysis between the treatment groups.

Mean cost of treatment

The mean overall cost of treatment was $33,715 (95% CI $30,013–$37,417) with everolimus 1.5 mg, $38,519 (95% CI $34,094–$42,943) with everolimus 3 mg and $36,509 (95% CI $32,430–$40,587) with MMF (Table 4). Differences between the three groups did not reach statistical significance.

Sensitivity analysis

One-way sensitivity analysis was undertaken for assessment of the effect that different assumptions might have on mean cost. Sensitivity analyses showed that the difference in costs between the two groups remained unaffected after estimated costs for nephrectomy were included, or after the UK unit cost vector was applied to all data so that the impact of variations in the cost vector could be tested.

Selection of the most appropriate drug for renal immunosuppression

As no significant difference was found in terms of efficacy between the two drugs, an adoption decision should be based on a cost-minimization approach. Since no significant difference was found in resource usage, this equates to selection of the cheaper

Table 2 Clinical outcomes at 6 and 12 months as percentage of patients. *P* values from one-way ANOVA were all non-significant

Outcome	Everolimus 1.5 mg ($n=194$)	Everolimus 3 mg ($n=198$)	MMF 2 g ($n=196$)
Biopsy-proven acute rejection, graft loss, death or loss to follow-up at 6 months	27%	26%	30%
Biopsy-proven acute rejection at 6 months	22%	18%	24%
Graft loss, death or loss to follow-up at 12 months	11%	17%	12%
Biopsy-proven acute rejection at 12 months	23%	20%	24%

Table 3 Resource use up to 12 months post-transplantation. Values in parentheses show 95% confidence intervals. *P* values from one-way ANOVA were all non-significant unless stated otherwise

Parameter	Everolimus1.5 mg ($n=194$)	Everolimus 3 mg ($n=198$)	MMF 2 g ($n=196$)
Mean total time hospitalized (days)	35.8 (31.2–40.4)	38.7 (33.6–43.8)	34.3 (29.5–39.1)
Mean number of biopsy procedures	1.1 (0.9–1.3)	1.2 (1.0–1.4)	1.0 (0.8–1.2)
Mean number of hospital outpatient consultations	0.7 (0.3–1.0)	0.5 (0.3–0.8)	0.4 (0.2–0.6)
Post-operative dialysis			
Patients (%)	21.6	27.3	26.5
Mean time on dialysis per patient (days) [a]	16.5 (6.8–26.2)	37.3 (22.9–51.7)	31.0 (17.7–44.3)
Additional immunosuppressive therapy (% patients)			
Prednisolone	40.2	42.4	44.4
Methylprednisolone	38.1	39.4	39.3
CsA	13.4	9.1	10.2
MMF	1.5	2.0	1.0
Tacrolimus	1.0	3.0	2.0
Mean total cumulative dose of CsA (mg)	74,066 (67,969–80,162)	68,424* (62,977–73,870)	83,450 (76,950–89,950)
Mean time on concomitant medication (days)			
Furosemide	64	54	39
Omeprazole	55	46	44
Nifedipine	38	27	26
Atenolol	31	23	23
Amphotericin B	18	25	16
CMV treatment	46	35	55
Lipid treatment	30	27	15

* $P=0.002$ versus MMF
[a]Includes all patients, with or without requirement for dialysis

Table 4 Mean resource costs per patient up to 12 months post-transplantation. Values in brackets show 95% CI values. All costs are expressed in 1996 PPP US dollars

Resource	Group 1 (1.5 mg Everolimus)	Group 2 (3 mg Everolimus)	Group 3 (2 g MMF)
Hospitalization	$17,394 ($15,172–19,615)	$19,133 ($16,440–21,826)	$16,871 ($13,976–19,66)
Diagnostic Procedures	$278 ($211–346)	$281 ($221–341)	$216 ($166–267)
Laboratory tests	$6,753($5,878–7,608)	$6,656($5,810–7,501)	$6,899($6,055–7,743)
Hospital outpatient consultations	$110 ($50–169)	$75 ($34–117)	$63 ($25–101)
Post-operative dialysis per patient[a]	$3,495 ($1,424–5,565)	$7,459 ($4,492–10,426)	$6,304 ($3,469–9,139)
Additional immunosuppressive therapy[b]	$105 ($53–157)	$63 ($37–89)	$87 ($49–125)
CsA	$4,454* ($4,055–4,854)	$4,124** ($3,769–4,480)	$5,163 ($4,722–5,604)
Concomitant medication	$1,127 ($750–1,504)	$727 ($530–925)	$906 ($672–1,139)
Mean total cost of treatment	$33,715 ($30,013–37,417)	$38,519 ($34,094–42,943)	$36,509 ($32,430–40,587)

* $P=0.04$ versus MMF
** $P=0.001$ versus MMF
[a]Includes all patients, with or without requirement for dialysis
[b]Excludes cost of everolimus and protocol-based use of MMF, CsA and prednisolone

drug. At present, the acquisition cost of everolimus is unknown.

Everolimus 1.5 mg has produced fewer graft losses in this study and could be the drug of choice, even at a higher acquisition cost than MMF, were savings due to fewer graft losses realized. However, this decision might be speculative, as the difference in graft survival was not statistically significant.

Discussion

This analysis of resource use and costs in the first 12 months post-transplantation demonstrates equivalent healthcare costs for everolimus 1.5 mg or 3 mg compared with MMF within a CsA-based triple-therapy regimen.

A lower total cumulative dose of CsA in the everolimus cohorts than in the MMF groups contributed to the difference in resource cost between everolimus 1.5 mg and the MMF treatment arms. This could be attributed to the synergistic mechanisms of action of everolimus and CsA, which facilitate a reduction in the dose of CsA.

These results highlight the need for long-term cost analyses when new immunosuppressive regimens are being assessed. The differences in mean total resource cost did not reach statistical significance over the course of this 12-month study; only long-term follow-up will provide a definitive answer to the question of whether use of everolimus results in significantly improved clinical outcomes and, thus, reduced healthcare costs over the lifetime of a graft. Within a 12-month time frame it would seem unlikely that any effect everolimus might have on the development of chronic rejection would be clinically important.

In addition to studies of longer duration, the use of everolimus within other regimens should be evaluated so that it can be established whether the trend shown in these results is sustained if different immunosuppressive strategies are used. In particular, everolimus, in combination with reduced-dose CsA, should be assessed, since initial results from this approach have shown a reduced incidence of side effects [11]. A Canadian economic model based upon these clinical results showed promising economic benefits for reduced-dose CsA in combination with Certican [12]. Additionally, economic outcomes associated with newer protocols, whereby everolimus is administered according to blood level monitoring instead of fixed dosage, should be undertaken.

Future studies will also be in a position to incorporate the relative costs of everolimus and MMF, which was not possible in this study; a marked disparity in price could be expected to affect overall treatment costs.

In conclusion, our results indicate that use of everolimus 1.5 mg, in combination with CsA microemulsion and steroids, does not influence treatment costs significantly if it is compared with MMF, during the first 12 months post-transplantation. Longer-term analyses, and an economic assessment of everolimus 1.5 mg with reduced-dose cyclosporine, should be undertaken so that the potential economic benefits of everolimus within a triple drug regimen following renal transplantation can be further understood.

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