SIMULATION USED IN CONJUNCTION WITH RANDOMISED CONTROL TRIALS TO EVALUATE THE COSTS AND BENEFITS OF A NEW DRUG

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ABSTRACT

A discrete event simulation approach called POST (patient oriented simulation technique) was used to evaluate the long term cost implications of prescribing a drug which has been shown to reduce the rejection rates of transplanted kidney during the first year after a transplant operation. The results indicated that the extra cost incurred in using the drug during the first years after transplantation, would be partially repaid by a reduction in the number of patients returning to dialysis.

1 INTRODUCTION

1.1 Patients with Renal Failure

Patients with endstage renal failure will die if they do not receive renal replacement therapy: either dialysis or transplantation. There are two main types of dialysis: hemodialysis, in which the patient makes regular use of a kidney machine to cleanse the blood, and peritoneal dialysis, in which the patient has a bag of fluid secured under their clothing and connected to the peritoneum to enable fluid exchange to take place. Either treatment must be continued indefinitely and incurs considerable expenditure. Renal transplantation requires an operation which is costly and, to some extent, risky. If the operation is a success, however, the patient can live a relatively normal life. Patients do need to take immuno-suppressant drugs to prevent transplant rejection. Such drugs are hazardous as they increase the risk of infection, bleeding and long term secondary malignancy. These start off at high doses and gradually level off to a maintenance dose. Rejection episodes may still take place, however, and are much more likely in the first year after transplantation. Patients may, with extra medication, recover from acute rejection episodes and retain their transplanted grafts. Some grafts do fail, and patients must return to dialysis, or may even die.

There has been considerable concern about the increasing costs due to the growth in the numbers of patients; there are increasing numbers accepted for treatment and continuing improvements in patient survival (Department of Health, 1996). There is general agreement that patients with functioning transplants both have a better quality of life and are cheaper to maintain, in the long term, than patients on dialysis. Most grafts are, however, obtained from cadavers and the supply is limited. It seems, therefore, that everything possible should be done to prevent graft rejection to enable patients to remain independent of dialysis as long as possible.

1.2 Anti-rejection Drug

The claims for a new anti-rejection drug, mycophenolate mofetil (MMF), which is on the market, are that it reduces the rate of early rejection of kidney transplants. Although it is now in use in a number of countries, the experimental conditions of the randomised control trials continued only for 12 months and therefore little is known about its long term effects on kidney graft survival. It is, however, expensive and those purchasing health care need to know whether the costs of buying MMF can be set against its effects in reducing transplant rejection and the use of hemodialysis or peritoneal dialysis, following transplant failure.

This is not a simple accounting exercise because of the way patients transfer between treatments and the different costs of the treatments. Simulation is a good vehicle for examining these because it takes into account the different treatment survival rates and modes of treatment.

1.3 Randomised Control Trials

Three randomised control trials (RCTs) which were double blind studies have reported on the efficacy of MMF. Two of the studies: the Tricontinental study (1996) and the US

study (Sollinger, 1995) used 2g MMF per day versus 3g per day versus azathioprine (AZA) with 1 to 2 mg/kg/day. The European study (1995) compared MMF to a placebo. All the patients in each study had corticosteroids and cyclosporin. The results indicated that MMF reduces acute transplant rejection and improves one year graft survival. Reviews of these trials recommended the use of 2g of MMF per day because there was lower toxicity compared with 3g of MMF. Although the studies had different characteristics, Halloran et al (1997) combined the results. Table 1 summarises the results for 2g MMF per day compared with the controls.

Table 1: Summary of Combined Randomised Control Trial Results (Halloran et al, 1997).

	Placebo/ AZA	MMF 2g
Number of subjects	492	501
Graft loss and deaths during one year	12.4%	9.6%
Deaths at one year	4.7%	4%
Patients who had suffered an acute rejection at one year	40.8%	19.8%

1.4 The Simulation Model

A simulation model, which has been used for planning services in England (Davies and Roderick, 1998), describes the progress of patients through treatment and is designed to estimate annual growth by modality from a base line starting position. The software used, POST (patient oriented simulation technique), is a set of procedures and functions in Pascal to provide the facilities of discrete event simulation. It is based on Pascal_SIM (Davies and O'Keefe, 1989), and has been extended for more complex problems (Davies, O'Keefe and Davies, 1993). The software is structured such that the entities can wait in more than one queue or take part in more than one event at the same time. The links between the records enable entity copies to be found instantly and withdrawn from queues or events, as necessary.

The flow of individual patients in the model is illustrated in Figure 1. In this study there was no distinction between the two types of dialysis. A patient entity starting dialysis is committed to a date of death and, depending on its suitability, put on the transplant waiting

list. If a suitable transplant arrives, it is withdrawn from dialysis and a date set for graft failure or death. Those that do not die are assumed to return to dialysis. Progress through treatment in the model is dependent, not only on resource availability, but also on individual patient characteristics and the time spent on treatment. New patient arrivals are given sampled characteristics.

The survival probabilities are split into two parts: the first year after a change in treatment, where survival may be relatively poor, and subsequent years, where survival is assumed to follow an exponential distribution. As simulated patients age, their treatment survival is recalculated when they cross age group boundaries.

Figure 1: The Flow of Patients through the Simulation

1.5 The Stages of the Study

The purpose of the study was to describe the progress of transplanted patients with and without MMF and to compare the progress and long term demands on resources from patients on renal replacement therapy. This was done in several stages:

- Designing a simulation, using data from the combined output from the three major randomised control trials (Halloran et al, 1997), to replicate a trial and to extend the results beyond one year;
- Designing a simulation to determine the long term effects and confidence limits of using MMF on a large population group, divided into age bands;
- Identifying the relevant costs from the literature and applying them to the output from the simulation.

2 DERIVATION OF THE INPUT DATA

2.1 Simulation of the Randomised Control Trials

The simulation described a 10 year cohort of patients receiving a transplant. The patients survived with a functioning graft, died or returned to dialysis. The dialysis survival data were the same as in previous studies (Davies and Roderick, 1998). Table 1 shows that the probability of dying was very similar in both arms of the trials. We assumed, therefore, that the probability dying in the first year was independent of the use of MMF. The first year graft and patient survival data were derived directly from the results of the randomised control trials.

Estimated long term graft survival for trial data - Control Arm. Given that patients survived for one year, the long term survival probability of the patients on control treatment was assumed to be the same as the probabilities for the whole UK population estimated from United Kingdom Transplant Support Services Authority (UKTSSA) data (Davies and Roderick, 1998).

Estimated long term graft survival for trial data - MMF Arm. A crucial part of the study is to estimate the long term survival of patients using MMF. We expect that their survival will be at least as good as the control arm. One important feature of treatment with MMF is that it shows a clear reduction in the number patients with acute rejection episodes (see Table 1).

A study by Tsai et al. (1993) indicated that long term graft survival was influenced by the number of acute rejection episodes in the first year after transplantation. We assumed that the reduction in acute rejections of patients on MMF would influence long term survival in the same way. The survival results from Tsai et al. were applied to figures for acute rejection episodes from the European study (1995) to get an estimate of relative long term patient survival for MMF and for the control arm of the study. The survival of patients on MMF, after the end of the first year, was estimated to be a multiple of 1.011 better per year than for patients in the control arm. This improvement was applied to the estimated survival of the controls (see Table 2).

2.2 Simulation of Renal Replacement Therapy in England

The simulation was designed to determine the effect of giving MMF, as opposed to conventional treatment, to transplanted patients from a large population group. The breakdown of patients by age and risk group was the same as in the Department of Health study (Davies and Roderick, 1998).

The data used were as follows:

- *Acceptance Data* The parameter chosen was 80 per million population, which is a low estimate of the 'need' (Davies and Roderick, 1998).
- *Transplant Data* Data from UKTSSA showed that there were approximately 30 transplants per million population in the United Kingdom in 1995. This number is unlikely to alter substantially unless the law changes or there is a considerable increase in the number of live related donations.
- *Initial Data for the Study* The Department of Health data (Davies and Roderick, 1998) were used to initialise the simulation.
- *Graft Survival Data and Probability of Return to Dialysis – assumed without the use of MMF* These data, broken down by age, were obtained from UKTSSA (1988 to 1996).

Table 2: Survival Data and Sources for RCT Simulation.

Percentage patients:	Control arm	MMF	Data Sources
with functioning grafts at one year	87.6	90.4	Combined RCTs
of those who 'fail' who restart dialysis in year 1	65.3	55.2	Combined RCTs and average death rates
with functioning grafts at two years	81.6	85.1	See text, para. 2.1
of those who 'fail' who restart dialysis after yr 1	57.1	57.1	UKTSSA data
survive dialysis at one year	92.5	92.5	Davies and Roderick, 1998.
survive dialysis at two years	86.5	86.5	Davies and Roderick, 1998.

Note: 'Failure' is defined as graft failure or death.

Derivation of Graft Survival Data using MMF: If p_i is the probability of graft failure or death in the MMF group and p_c the probability of graft failure or death in the control group, then, the relative risk of graft failure or death with MMF at one year = $p_i/p_c = 9.6/12.4 = 0.774$. The confidence limits of the relative risk were found to be (0.541, 1.106) for the pooled results. It appears therefore that there is a small probability that MMF is not improving survival at all.

The relative risks were then applied to patient survival in each age group in order to estimate the effects of using

MMF on the whole population of patients receiving transplants. (Note: we did not distinguish between AZA and other non-MMF treatments). If p_{ac} is the probability of graft failure or death at one year in age group a for the control group, c , based on data from UKTSSA, then the one year survival probability for those in that age group treated with MMF, was assumed to be: $q_{at} = 1 - 0.774 p_{ac}$.

The probability of failure after the end of the first year was calculated in the same way as that shown in Section 2.1, based on the results from Tsai et al (1993). That is, the probability of survival each year by age group after the end of the first year was estimated from the UKTSSA data and multiplied by 1.011. Table 3 shows the values for a sample age group.

Derivation of Probability of Return to Dialysis for MMF group: The death rate in each age group was assumed to be independent of the use of MMF. If the probability of dying in age group a was d_a , then the probability of surviving and returning to dialysis in the first year, given that the patient had 'failed' = $(1 - d_a / p_{at})$.

The probability of surviving and returning to dialysis after 'failure' was lower for the MMF patients during the first year, than for the control group (see Table 3), because the denominator, p_{at} , was larger and the death rate, d_a , the same. After the first year the probability was assumed to be the same for all patients, regardless of their use of MMF.

Table 3: Survival Probabilities used in the Simulation for Age Group 55 to 65 years.

Probability of :	Year 1	Year 2 +
Annual graft survival		
- without MMF	0.750	0.908
- with MMF	0.806	0.918
Patient surviving and resuming dialysis after failure:		
- without MMF	0.560	0.303
- with MMF	0.432	0.303
Annual survival on dialysis	0.827	0.854

'Failure' is defined as a graft failure or death.

2.3 Cost Data

The most recently published cost data for the United Kingdom were collected in Manchester (Mallick, 1997). Costs do vary considerably and so these costs can be regarded as only approximate (Table 4). The cost of treating a patient with MMF for a year is assumed to be: £2490 (Personal Communication, Roche Products Ltd).

Table 4: Approximate Costs from Manchester

Functioning Grafts per year	£4000
Dialysis per year	£21000
Transplants -each	£11600

3 SIMULATION RESULTS

3.1 Simulation of the Randomised Control Trials

This simulation showed that with a randomised control trial of 500 patients in each arm, the MMF groups might expect, on average, fewer rejections and fewer people on dialysis. There would be a reduction in deaths in MMF cohort because the annual survival rate of patients with a functioning graft was estimated to be better than for those on dialysis (see Table 5).

Three year patient survival from the simulation validated well against results from the USA trial (Tomlanovich et al, 1997) with simulation results of 76.0% and 80.1% for MMF and AZA compared to 75.0% and 81.2% respectively from the USA trial. Death rates were 11.2% and 10.1% from the simulation compared to 11.6% and 10.3% from the trial.

Table 5: The Five-year Results of Simulating the RCTs with 500 Patients in each Arm and 500 Replications.

	Control	MMF	Difference
Functioning Grafts	330	355	-25
Dialysis	83	67	15
Failed Grafts cumul.	102	82	50
Deaths cumulative	88	78	10

3.2 Simulation of Patients on Renal Replacement in England

Figure 2 shows how the use of MMF is likely to decrease the number of dialysis patients and increase the number of patients with functioning grafts in a population of 10 million people. Figure 3 shows how the use of MMF may, in addition, reduce the expected number of graft failures and deaths. The death rates fall because the long term survival probabilities for patients with functioning grafts are better than for those on dialysis.

3.3 Costs of Output

Figure 4 shows the cost implications of using MMF as a continuous therapy. The use of MMF leads to a net increase in costs but the additional cost of the MMF is almost exactly balanced by the decreased cost arising from treating fewer dialysis patients.

Simulation to Evaluate the Costs and Benefits of a New Drug

Figure 2: Projected Numbers of Patients on Dialysis and Transplantation over the next 10 Years for a Population of 10 million.

Figure 3: Simulation Results showing the Change Expected by using MMF rather than Pre-existing Treatments for Transplants in a Population of 10 million.

Figure 4: Simulation Results showing the Change Expected in Costs in using MMF rather than Pre-existing Treatments for Transplants in a Population of 10 million.

As no additional costs have been attributed to acute rejections, failed transplants or deaths, these results provide a conservative estimate of the probable cost benefits

4 CONCLUSIONS

This paper describes a methodology for evaluating new treatments for chronic patients. In order to model the system, we had to derive the long term survival of patients on the new treatment. We did this by deriving the survival of patients on pre-existing treatments and then relating long term survival to events occurring during the first year; in this case it was the number of acute rejections.

This approach, using simulation, does provide a way of evaluating health benefits in terms of patient survival and types of treatment and of looking at the long term cost implications. Although the cost estimates are crude, it appears that the use of MMF will cause the Hospital Trusts and Health Authorities to incur some extra expenditure. The cost savings arising from the reduced use of dialysis will, however, go a long way towards balancing these extra costs out. It also appears that the use of this drug may, in time, lead to a reduction in deaths. Simulation provides a way of bringing together different sources of data and evaluating them together.

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REFERENCES

- Davies R., and R. M. O'Keefe. 1989. *Simulation modelling with Pascal*. Prentice Hall Int (UK).
- Davies R., R. M. O'Keefe, H. O. Davies. 1993. Simplifying the modeling of multiple queuing, multiple activities and interruptions, a low level approach. *ACM Transactions on Modeling and Computer Simulation* 3(4): 332-346.
- Davies R, P. Roderick. 1998. Planning resources for renal services throughout UK using simulation. *European Journal of Operational Research* 105: 285-295.
- Department of Health. Health Care Strategy Unit. 1996. *Review of Renal Services. Part II: Evidence for the Review*. London Department of Health
- European MMF Co-operative Study Group. 1995. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for the prevention of acute rejection. *The Lancet* 345: 1321-1325.
- Halloran P., T. Matthew, S. Tomlanovich, et al. 1997. Mycophenolate mofetil in renal allograft recipients. *Transplantation* 63: 39-47.
- Mallick N. P. 1997. The costs of renal services in Britain. *Nephrol Dial Transplant* [Suppl. 1], 25-28.
- Sollinger HW for the US Renal Transplant MMF Study Group. 1995. MMF for the prevention of acute rejection in primary renal cadaveric allograft recipients. *Transplantation* 60: 225-232.
- The Tri-continental MMF renal trans-plant study group. 1996. A blinded randomised clinical trial of MMF for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 61: 1029-1037.
- Tomlanovich S., S. Cho, E. Hodge, J. Miller, J. Neylan, I. Hoofman, M. Rees. 1997. Mycophenolate mofetil in

cadaveric renal transplantation – 3-year data.
American Society of Transplant Physicians, 16th
Annual Meeting, (Abstract only)

Tsai R. J., M. L. Henry, E. A. Elhammas, R. M. Ferguson.
1993. Predictors of long-term primary cadavaric renal
transplant survival. *Clin Transplantation* 7: 345-352.

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