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David Talbot
K. Suddeke Reddy
David Watson
Henry Pleass
John L. R. Forsythe
George Proud
R.M. Ross Taylor

Developing the ideal immunosuppressive protocol by internal audit

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D. Talbot (✉) · K. S. Reddy · D. Watson
H. Pleass · J. L. R. Forsythe · G. Proud
R.M. Ross Taylor
Renal Transplant Unit,
Royal Victoria Infirmary,
Queen Victoria Road
Newcastle upon Tyne NE1 4LP, UK
Fax: + 44 91 233 1364

Abstract To identify the best immunosuppressive protocol in a centre where five different regimens are employed, 227 consecutive renal recipients who were transplanted over a 2.5-year period were studied. The five different regimens employed were cyclosporin monotherapy, dual therapy (cyclosporin and prednisolone), triple therapy (cyclosporin, azathioprine, prednisolone), antithymocyte globulin (ATG) followed by dual therapy and ATG followed by triple therapy. Recipients were chosen for the different regimens according to HLA mismatch, positive donor crossmatch due to IgM, regraft and delayed graft function. The group with the lowest risk, cyclosporin monotherapy, had the highest acute rejection rate, with only 13 % free of acute rejection (in comparison to triple immunosuppression, $P = 0.024$, chi-square test). The overall infection rate and graft success rate were similar between the different groups.

Key words Immunosuppression, renal transplantation · Renal transplantation, immunosuppression · Audit, immunosuppression

Introduction

The design of an immunosuppressive protocol to maintain a minimum effective level of immunosuppression has always been the goal of the Newcastle Renal Transplant Unit. This protocol was based initially on the donor/recipient mismatch, but other factors such as the presence of donor T cell-directed IgM and regraft were subsequently incorporated as risk factors. The lowest risk group was treated with cyclosporin monotherapy postoperatively and the highest risk group received a 10-day course of antithymocyte globulin (ATG) followed by triple immunotherapy (azathioprine, prednisolone, cyclosporin). It was felt that with the presence of varied immunosuppressive protocols, not only was it important to audit the total graft outcome but also to know the incidence of treatable rejection. This information has become increasingly relevant since the association of early acute rejection and chronic graft nephropathy later [1, 2, 5, 11].

Patients and methods

A total of 227 renal recipients were reviewed retrospectively to determine risk factors at the time of transplantation. The recipients were subdivided according to the immunosuppressive protocol they received in consequence of their risk factors. The original protocol is illustrated in Table 1. In general, good matches were prescribed cyclosporin monotherapy (better than 1,1,1 mismatch). Medium matches, equal to 1,1,1 mismatch, received dual therapy (cyclosporin and prednisolone). Poor matches (worse than 1,1,1) received ATG (Merieux), followed by triple therapy (cyclosporin, azathioprine, prednisolone). Recipients with a history of a previous failed transplant cumulated an additional risk factor such that a well-matched regraft kidney (better than 1,1,1 mismatch) was given dual therapy.

Triple immunosuppression (cyclosporin, azathioprine, prednisolone) was used mainly for those combinations where donor T lymphocyte-directed IgM was detected. ATG followed by dual therapy tended to be used mainly as a part of trial for recipients in established delayed graft function, immaterial of the match.

All recipients received 500 mg of methylprednisolone prior to completion of the vascular anastomosis and the dosage was repeated 24 h later. Cyclosporin, when used as mono, dual or triple

Table 1 Newcastle immunosuppressive protocol

All patients 500 mg methylprednisolone at clamps off repeated at 24 h
1 Immunological failure or 1A 1B 1DR mismatch: CyA + Prednisolone 25 mg
2 Immunological failures: Triple therapy + Cotrimoxazole
Positive historical or current T-cell crossmatch; negative after dithioerythritol treatment (IGM) therapy: Triple therapy + Cotrimoxazole
Poor match; Worse than 1A 1B 1DR: ATG + Prednisolone 25 mg CyA at day 7 Azathioprine day 9 Cotrimoxazole
All others Cyclosporin commencing at 24 h post-transplant

therapy, was commenced the day after transplantation. Initially, this was commenced at an oral dosage of 10 mg/kg per day, but in the second half of the study this was reduced to 8 mg/kg per day. Dosages were altered to achieve serum trough levels of 200–400 ng/ml for monotherapy and 200–300 ng/ml for triple therapy. Early control of cyclosporin to within these levels was quite rigorous whilst the recipient was on the unit, but subsequently the patients were monitored by their referring centres where different levels were accepted.

Preoperative risk factors leading to the recipients being ascribed to the different immunosuppressive protocol groups are shown in Table 2. The cyclosporin monotherapy group was the largest with 98 patients. The triple immunosuppressive regimen was the second largest with 50. The dual therapy group had a significantly poorer match than the monotherapy group ($P = 0.007$, Mann-Whitney U-test). The triple immunosuppressive group had an increased incidence of positive T-cytotoxic crossmatch rate due to IgM antibodies (44 %, $P < 0.0001$, chi-square), and the regraft rate was also higher than in the monotherapy group (22 %, $P = 0.0016$, chi-square test). The ATG with dual therapy group was similar to the monotherapy group for mismatch as the decision to use it depended on delayed graft function. The ATG with triple therapy group revealed the poorest match, the highest regraft rate (36.8 %) and generally an increased level of donor-directed IgM (21 %). These findings showed that the selection criteria for the different regimens were adhered to.

Patient follow-up

Follow-up data were obtained by contacting the referring centres by phone. Outcome was assessed at three monthly intervals with the shortest follow-up of 3 months and the longest 2 years.

Rejection was defined as a deterioration in creatinine requiring treatment with methylprednisolone which, in most but not all cases, was accompanied by histological confirmation. Rejection episodes were defined as separate when they occurred more than 7 days after finishing an antirejection treatment course.

Data analysis

Risk factors of donor, recipient age, regraft, mismatch and ischaemic times were determined for each transplant. Outcome of the transplant was determined relating to recipient death, graft failure, duration of delayed graft function, rejection episodes, dosage of methylprednisolone (1 unit = 250 mg methylprednisolone) and requirements for ATG.

The data was analysed using the chi-square test for incidence in the different groups (e.g. percentage free of rejection) or the Mann-Whitney U-test for the non-Gaussian distribution of number of rejection episodes per patient and dosage of methylprednisolone.

Results

The outcome of these different patient groups is revealed in Table 3. No statistical difference in death or graft failure was found between the different groups. The triple therapy group had probably an artificially high failure rate at 18 % as, in half of the cases, the failure was due to either technical failure or nonfunction. Primary function was obviously lowest in the ATG with dual therapy group where it was used primarily for nonfunction.

The incidence of rejection was found to be highest in the group that was considered the lowest risk (cyclosporin monotherapy). Here only 13 % of cases were free of rejection in comparison to the triple therapy group where 30 % of cases were free of rejection ($P = 0.024$, chi-square test). The steroid requirement for the monotherapy group was 6.7 pulses of 250 mg methylprednisolone in comparison to 5.8 pulses for the triple therapy group though significance was not achieved ($P = 0.12$, Mann-Whitney U-test). This difference was even more pronounced when regrafts and living related

Table 2 Donor/recipient background contribution to the risk factors used to define the subsequent immunosuppressive regimen

Therapy	*n*	Donor age (years)	Recipient age (years)	Living related (%)	Regratt (%)	T current IgM (%)	A/B/DR mismatch	Cold ischaemic time (min)
Mono	98	41.4	44.5	3	2	6	2.3	1250
Dual	38	48.7	44.3	7.9	15.8	5	2.8	1228
Triple	50	40.9	43.9	4	22	44	2.1	1294
ATG + dual	22	41.6	52.3	0	0	0	2.5	1483
ATG + triple	19	36.4	41.3	5.3	36.8	21	4.2	1420

Table 3 Outcome relating to the different immunosuppressive groups

Therapy	*n*	Death (%)	Graft failure (%)	Primary function (%)	Rejection episodes	Methyl-prednisolone (250 mg)	Rejection-free (%)	Infection (%)	
								minor	major
Mono	98	2	8	79.6	1.2	6.7	13	14	10
(Failures 6 immunological; 2 technical)									
Dual	38	5	8	39	1.1	5.7	23	16	5
(Failures 3 immunological)									
Triple	50	6	18	58	0.9	5.8	30	10	10
(Failures 5 immunological; 2 technical; 2 primary nonfunction)									
ATG + dual	22	0	13.6	27	0.6	3.3	36	4.5	9
(Failures 1 infection; 2 primary nonfunction)									
ATG + triple	19	5	15.8	47.4	0.7	3.3	37	5.2	5.2
(Failures 2 immunological; 1 primary nonfunction)									

transplants were excluded. The proportion free of rejection remained the same in the monotherapy group (13 %), but with triple therapy the percentage increased to 38 % ($P = 0.0032$, chi-square test). Similarly the steroid requirement was reduced to 4.4 pulses of 250 mg methylprednisolone in the triple therapy group in comparison to 6.5 for the monotherapy group ($P = 0.017$, Mann-Whitney U-test). Of the 98 monotherapy patients who started on this treatment, only 45 left hospital on this regimen, the remainder having converted to dual or triple immunosuppression (conversion occurring if ATG was required as a second line therapy for monotherapy or dual therapy, or if the first rejection episode occurred under 5 days post transplant).

The number of rejection episodes was further reduced when ATG was used either with dual or triple therapy in stepwise progression, with pulsed steroid requirement also being reduced.

Interestingly, the overall infection rate from increasing immunosuppression protocols was not increased. There was a tendency toward increasing the proportion of serious infections in comparison to minor ones with the increasing immunosuppressive protocols. Serious infections included CMV and septicaemia; minor infections were urinary tract infections, phlebitis and wound infections.

Discussion

The variation in immunosuppressive protocols used by different renal transplant centres is legion. However, cyclosporin monotherapy is only used by a relatively small number of centres [3, 10]. Randomised trials have been performed revealing similar outcomes between triple therapy and monotherapy. However, treatable rejection was more prevalent in the monotherapy groups and infection more common in the triple therapy groups [3, 9], with the problem of cyclosporin nephrotoxicity occurring particularly in those grafts with delayed graft function [6, 9].

Solutions have been sought in two ways. First, by tailoring the immunosuppressive protocols to the recipients' needs regarding mismatch and delayed graft function, it was possible to maintain a lower level of immunosuppression. Second, by adopting multiple drug regimens (triple or quadruple), a lower level of each agent was required to avoid toxicity.

The theoretical benefits of a tailored regimen are to reduce infection and the risk of neoplasia. The disadvantage of such a system is that it is complex, it introduces too many variables and it may give rise to increased treatable early rejection [3, 4]. With increasing evidence of the association of early acute rejection and poor long-term outcome [1, 2, 11], it seems mandatory that an effort be made to minimise early acute rejection. The benefits of a triple immunosuppressive regimen are that it is easy to apply and that toxic levels of each are minimised as less is required. In addition, triple therapy can be converted to dual or monotherapy with time, whereas in the case of monotherapy there is a 50 % conversion rate. Among the disadvantages is the fact that the infection rate can be increased with triple immunosuppression [3, 9]. The fact that we found our infection rate to be the same means that this reason not to use triple immunosuppression does not apply at our centre. The longer term complication of neoplasia could still be pose a problem for triple immunosuppression, and the audit of immunosuppressive regimens should be continued to determine this [8]. Unfortunately, this supposedly simple approach of triple immunosuppression can be complicated by varying the levels of cyclosporin which can account for some variation in long-term outcome [7].

It is evident, therefore, that like the number of different immunosuppressive protocols, the number of papers describing the „ideal" protocol are also numerous. Con-

sequently, the important conclusion that should be drawn from this paper is not necessarily that monotherapy should not be used because of its almost universal early acute rejection and equal infection rate with triple immunosuppression. Rather it is that any centre that has a tailored approach to its immunosuppression should regularly audit their results to ensure that the best regimen is used to produce reduced rejection with the lowest infection rates.

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