A COMPARISON OF TWO APPROACHES TO THE PROBLEM OF EARLY ACUTE REJECTION OF RENAL TRANSPLANTS

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Summary

This study compares the effects of two different approaches to the problem of early acute rejection of renal transplants.

The results of a ‘conventional’ approach in which acute rejection is diagnosed and then treated are compared with those of a ‘trial’ group in which prophylactic anti-rejection therapy is given in the form of high dose oral steroids.

Methods

In the conventional ‘group’, renal allograft recipients were treated with 60mg of prednisolone per day for the first week post transplantation, reducing stepwise thereafter. Azathioprine was given in a normal dose of about 2mg/kg. When acute rejection occurred, it was treated with three grams of intravenous methyl prednisolone.

On occasions, when there was no response to this and the biopsied kidney showed severe vascular changes, heparin was also given.

In the ‘trial’ group, renal allograft recipients from day three received high doses of oral steroids, reducing stepwise, and normal doses of azathioprine. Twenty-one patients received a daily dosage schedule of 60mg, 60mg, 60mg, 200mg, 200mg, 175mg, 175mg, 150mg, 150mg, 125mg, 125mg, 100mg etc of prednisolone.

Ten patients received a daily dosage schedule of 30mg, 30mg, 30mg, 200mg, 30mg, 200mg, 30mg, 150mg, 30mg, 150mg, 30mg, 100mg, 30mg, 100mg, 30mg, 60mg, 30mg etc of prednisolone.

On occasions, when there was severe acute rejection or subsequent acute rejection, intravenous methyl prednisolone was also given; heparin was occasionally used as in the conventional group.

Sixty-three consecutive first and second cadaveric grafts are considered, one graft from the conventional group was excluded as it suffered arterial infarction within 24 hours, leaving 31 in each group. The donors ranged in age from 8 – 66, the recipients from 13 – 57. The groups were comparable regarding age, sex and
tissue matching (average 2 HLA mis-matches).
Nine patients in the ‘conventional’ group and 5 patients in the ‘trial’ group
had not had prior blood transfusions.

Results

Results were assessed at 12 weeks regarding patient mortality, graft loss, and
morbidity.
There were no technical graft failures.

Mortality

One patient in the ‘conventional’ group died from septicaemia and gastro-intestinal
haemorrhage following removal of a rejected graft. No patient died in the ‘trial’
group.

Graft loss

Twelve grafts were lost from rejection in the conventional group, three in the trial
group, all of which had received the high doses of steroids. This gives twelve week
graft survival figures of 61%, and 90% respectively.

Morbidity

Although ‘steroidal facies’ is difficult to quantify, it did appear to be worse in the
high dose ‘trial’ group and similar in the others (as might be expected, as the total
dose of steroids was similar).
Wound infection rates with the graft in situ were 1 in the ‘conventional’, and
3 in the ‘trial’ group. There were nine wound infections in the ‘conventional’ group
following removal of rejected grafts, none in the ‘trial’ group.
Viral infections were similar (3 and 4 respectively).
Three patients in the conventional group suffered gastro-intestinal haemorrhages,
2 in the trial group.
Local bleeding probably reflecting the use of heparin, occurred in 2 patients in
each group.
Secondary bleeds following graft removal occurred only in the conventional
group (4).
Induction of mild diabetes was similar in each group (3 patients). (When non-
transfused patients are excluded, the graft survival rates become ‘conventional’
68% (15 out of 22) and ‘trial’ 96% (25 out of 26).
Since the trial has been terminated, a further 14 patients have been transplanted
at least 12 weeks ago and managed as in the ‘trial’ group with the lower dosage.
No grafts have been lost from rejection. One patient died with a functioning graft
from septicaemia after leakage of a pyloroplasty.
A total of forty-five patients have received the ‘trial’ regime. If non-transfused
patients are excluded, the mortality has been one out of forty (2.5%) and the re-
jection rate one out of forty (2.5%).

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Discussion

Many drugs have been used in an attempt to reduce early acute rejection of renal transplants. However, apart from Cyclosporin A, Steroids and Azathioprine remain the drugs of choice. The method in which these are used is a subject of controversy. Recently it has become apparent that low initial doses of oral steroids are as effective, or more effective than high initial doses [1,2].

Our results suggest that in our unit we have been able to reduce the incidence of graft loss from early acute rejection without increasing mortality or morbidity by adopting a regime of prophylactic anti-rejection therapy with high dose oral steroids. The lower dosage schedule would appear to be as effective, or more effective than the higher dosage schedule (which we would not now recommend). The total dose of oral steroids given to all our patients is now similar to that given to the majority of patients at Belfast — 20mg of prednisone initially, but increased to 200mg where rejection is diagnosed [1].

We would stress that our results refer to early acute rejection. Although in the medium term our results appear to be maintained, the long term results and morbidity are not known. The regimen would appear however to be a safe and effective way of reducing early acute rejection and is particularly suitable for grafts suffering acute tubular necrosis whose rejection may be difficult to diagnose, and where Cyclosporin A is probably contraindicated.

References

1  McGeown M et al. Transplantation 1980; 29: 287

Open Discussion

BARNES (Birmingham) Could you tell me how you randomised your patients between the two groups?

PENTLOW The patients were not randomised and I am not claiming that they were. They were allocated according to which night of the week the patients came in. They were drawn from a common pool. The surgery by and large was done by different surgeons. They were managed by a common group of doctors post-operatively. There were no technical exclusions. I accept your point but I think if you compare these trial groups in most respects they are comparable.

McGEOWN (Belfast) You mentioned our steroid dosage. You did not give, in your summary, your basic steroid dosage, so I only had time to do a rapid calculation but it seems to me that you must give considerably more steroid than we do in the first month.

PENTLOW Initially we give 30mg of prednisolone as opposed to 20mg. When your patients develop acute rejection they are given a dosage schedule which is
identical in terms of total dosage to the schedule of all steroids which all our patients are getting, so that our patients are getting a similar dose to those of yours that have suffered acute rejection.

McGEOWN Yes, but you then continued if they rejected, to give them further steroid I think.

PENTLOW If they had severe acute rejection. If it was a mild episode we would sit it out. If they had severe acute rejection then we would give intravenous methyl prednisolone.

McGEOWN Well as I say, I had no time to do this sum in detail but I am pretty certain that I can bear this out, that you use more steroid than we do. I say this only because you used the comparison.

PENTLOW I know we actually use more steroids; I have said the total dosage was not enormously greater than yours, which it is not, apart from the fact that we use methyl prednisolone in addition on occasions.

JEEKEL (Rotterdam) Your survival at three months of group 1 was a low 61%. Were there many technical failures or was it immunological?

PENTLOW No there were no technical exclusions at all. All the grafts which were lost were lost due to acute rejection.

JEEKEL How did you prove that?

PENTLOW By examining them histologically.