Minimising the Risks of Treating Acute Allograft Rejection

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Summary

The risks of treating allograft rejection are primarily related to high-dose steroid therapy. To determine when the possible benefit of anti-rejection therapy might not justify the risks, we analysed 20 severe acute rejection (SAR) episodes for indices of reversibility. Prior renal function was similar in all patients. $C_{cr}$ fell to 10 ml/min or less, but degree of renal dysfunction was not predictive of reversibility, nor were time since transplant, oligo/anuria, proteinuria, or hypertension. The only consistent finding was that function began to improve in reversible rejection 3.8 ± 1 days after beginning therapy. Our rejection treatment, based on this finding, is to use gram doses of IV prednisolone, up to three times in five to seven days. Among 41 patients with 45 grafts so treated, there was no fatality or gastrointestinal haemorrhage. Other complications (fistulae and/or infections) were related to total dose and frequency, to intensive therapy during severe renal dysfunction or to urinary leaks. Limitation of the period of high-dose steroid therapy was associated with reduced morbidity and mortality in renal allograft recipients.

Introduction

Morbidity and mortality in renal-transplant recipients appear to be related to immunosuppressive therapy (Hill et al, 1967; Moore and Hume, 1970) particularly high-dose steroid therapy for acute allograft rejection. The triad of rejection, immunosuppression and sepsis is identified with 55% of renal-transplant recipient deaths in the Tenth Registry Report (1973). The magnitude of the risk, the deaths of 40% of recipients within three years (Eleventh Registry Report, 1974), is such as to minimise the advantages of cadaveric kidney transplantation over regular haemodialysis.

This study was made to assess the risk or benefit in treating acute rejection. The available literature (Dossetor et al, 1967; MacLean et al, 1969; Silcott et al, 1972; Williams et al, 1967) was unhelpful in determining when further therapy might be unwise. First, 20 episodes of severe acute rejection (SAR) were analysed.
for characteristics that might be prognostic of reversibility. Second, all rejection episodes treated with IV prednisolone were analysed to find guidelines to safer anti-rejection therapy.

PATIENTS AND METHODS

Reversibility of Severe Acute Rejection

Thirty-nine patients, aged 14–48, received 42 renal allografts, 24 from living related donors (LRD) and 18 from cadavers (CD), from January 1969 to December 1971. All patients were started at the time of transplantation on azathioprine 1.7–2.5 mg/kg body weight daily, and prednisone. The prednisone regimen, initially 25 mg four times daily, was modified to a single morning dose daily by 10 days post-transplant. It was gradually reduced to an alternate-day schedule as previously reported (Siegel et al, 1972).

Alternate-day therapy was interrupted in favour of higher daily dosage upon diagnosis of rejection. Blood and urine test were performed daily in hospital following transplantation and during anti-rejection therapy.

Rejection was usually first detected by changes in serum creatinine concentration or creatinine clearance. Serial radioisotopic studies of renal blood flow with m99 pertechnetate and 131 iodohippuran (Aquino et al, 1971) were used to discriminate between ureteric and vascular obstruction, rejection and post-transplant acute renal failure (ATN). Renal biopsy was not used routinely for diagnosis of rejection, but histology was examined in all patients before graft nephrectomy.

SAR was defined as episodes in which Cr fell to 10 ml/min or less within a week. There was no hyperacute rejections. Baseline data never predicted impaired function by more than a week.

Treatment of all but one episode included an increase in prednisone dosage to at least 100 mg/day in nine cases treated before June 1970, and with intravenous boluses of 0.5 to 1 g of prednisolone in 10 treated after June 1970. Heparinization (Kincaid-Smith, 1969) was included in the treatment of 17 episodes, four of which were also treated with dipyridamole. Graft X-irradiation (150 rad × 3) was used seven times.

After completion of successful therapy, patients were followed up for about 18 months (range 11–32 months).

Consequences of Prednisolone Therapy

One gramme doses of prednisolone as anti-rejection therapy (Bell et al, 1971) were started in June 1970. The standard three-gramme course was repeated as necessary for recurrence of rejection.

Fifty-six patients aged 14–52, comprising 39 males and 17 females, received 60 renal allografts (34 LRD, 26 CD) between June 1970 and June 1974. Rejection
episodes in 45 grafts (24 LRD, 21 CD) in 41 of these patients were examined to
determine the relationship of steroid dosage to outcome. Follow-up continued
for 2–49 months (27 ± 13, mean ± SD). Ten rejection episodes in eight patients
of the SAR group were included. The criterion for inclusion was treatment with
at least two 0.5 g or one 1 g IV prednisolone dose.

RESULTS

Reversibility of Severe Acute Rejection (SAR)

SAR was common with little difference in frequency between LRD and CD grafts.
Six of 24 LRD grafts (23 patients), including two of eight A-match LRD pairs, and
six of 18 CD grafts (16 patients) were affected. None had rejection episodes before
those reported here.

20 SAR episodes were treated, 12 in six LRD and eight in six CD recipients.
Time of onset was 5–61 days after transplantation in all but one patient (footnote,
Table I). All 12 episodes in LRD recipients and four of eight in CD recipients were
reversible.

Creatinine clearances before rejection in LRD and CD patients were not signifi-
cantly different (mean \( C_{Cr} \pm SD = 37.8 \pm 12 \text{ ml/min in LRD and } 35.5 \pm 9 \text{ ml/min in CD recipients} \)). The range of creatinine clearances before rejection was 18–60
\text{ ml/min in the LRD group and 20–50 ml/min in the CD group.}

Full recovery of function occurred in seven of the eight patients (6 LRD and
2 CD). One LRD recipient, B.H. (Table I) suffered two attacks of SAR, 18 and
25 months after transplantation. Mean \( C_{Cr} \pm SD in the other seven patients was
43 ± 9 ml/min before SAR and 63 ± 17 ml/min after 7–32 months follow-up;
mean difference ± SEM was 20.6 ± 6.6, \( p < 0.025 \).

No deaths related to transplant rejection or its treatment occurred in these
12 patients either during the treatment of rejection or follow-up. Serious infections
occurred during the treatment of five patients. There was one occurrence each
of pneumocystis carinii pneumonia, Gram-negative pneumonia, scrotal urinary
fistula with epididymitis, monilial oesophagitis, and pneumococcal pneumonia.

Reversibility Indicators Reversible and irreversible SAR episodes were compared
to find distinguishing characteristics (Table I), but they were similar in the time
after transplantation, function before and during rejection, and percentage reduc-
tion of function. Oliguria occurred in all the irreversible rejections and transiently
in six out of 16 reversible SAR's. Heavy proteinuria (2.5–9 g/day) and hypertension
occurred equally in both groups. Concurrent oliguria and fever were ominous
but unreliable signs because of the many possible causes of fever. Three LRD grafts
recovered at least partially from two SAR's and one had full recovery after at
least four.

The outstanding characteristic of reversible rejection was that improvement in
TABLE I. Characteristics of 20 Severe Acute Rejection Episodes in 12 Patients (6 LRD, 6 CD)

<table>
<thead>
<tr>
<th></th>
<th>Reversible</th>
<th>Irreversible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Onset (days post-op)</td>
<td>6–52*</td>
<td>5–30</td>
</tr>
<tr>
<td>Ccr pre-rej’n, ml/min**</td>
<td>38.8 ± 12</td>
<td>34.5 ± 6</td>
</tr>
<tr>
<td>Olig/Anuria</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Fever + Oliguria</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Response, days</td>
<td>3.8</td>
<td>---</td>
</tr>
</tbody>
</table>

* With two exceptions in one patient, at 18 and 25 months.
** Up to 9 g/day.
† ≥ 120 mm Hg diastolic blood pressure.

function took place two to five days (3.8 ± 1.0, mean ± SD) after beginning treatment in 15 of 16 instances, while no sustained decrease in serum creatinine (≥ 20%) or increase in Ccr occurred in irreversible rejection. Failure to improve after five days of intensive therapy carried a poor prognosis.

Five grafts were biopsied, of which three showed irreversible damage, one showed resolving rejection, and another had kanamycin nephrotoxicity.

Consequences of Gram Dose Prednisolone Therapy

Forty-five grafts (24 LRD, 21 CD) were at risk in 41 patients. Those who received 1, 2, and 3 g (Groups A, B, C in Table II) were treated over a brief span for a solitary rejection episode, while those in Groups D, E, F were treated for longer.

TABLE II. Relationship of Prednisone Treatment and Complications with 45 Grafts (24 LRD, 21 CD) in 41 Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (total grammes)</th>
<th>Grafts treated</th>
<th>Time span (days rx)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>4</td>
<td>3–10(5.4)</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>9</td>
<td>4–9(5.3)</td>
<td>4</td>
</tr>
<tr>
<td>D</td>
<td>2.5–3.5</td>
<td>6</td>
<td>14–27(24)</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>4–6</td>
<td>10</td>
<td>9–51(23.5)</td>
<td>6</td>
</tr>
<tr>
<td>F</td>
<td>7–10</td>
<td>4</td>
<td>36–56(48)</td>
<td>2</td>
</tr>
</tbody>
</table>

In spite of the incidence of morbidity, there were no deaths. All but four patients have been followed at least six months (29 ± 15, mean ± SD) and there have been no instances of femoral head necrosis.

The patients who received 1 or 2 g (Groups A and B) had one bladder fistula in each group and herpes zoster in a Group A patient. In Group C (3 g in 5.3 days) there was more morbidity. The Group C complications were a wound infection,
a bladder fistula, a ureteric fistula with severe wound infection, and fever from non-pneumonic cytomegalovirus infection.

Group D and C patients received similar total prednisolone dosage, but over a period three to five times longer in D, and with less frequent complications.

Group E patients were treated with 4 to 6 g (mean 4.65g) over periods varying from nine to 51 days. When ranked according to the mean interval between doses, all six complications occurred in those with a mean interval of less than 5.5 days. These consisted of three wound infections, one with vascular anastomosis disruption, a urinary fistula, a case of oropharyngeal thrush and a septic pyelonephritis.

Urinary leakage or bacteriuria antedated most of the severe infections and urinary fistulae even in patients with limited steroid exposure (Groups A, B, C).

**Patient and Graft Survival**

Patient mortality was nil despite substantial morbidity. None of the 24 LRD grafts was lost acutely. Three LRD and four CD grafts suffered chronic rejection, which in our experience has never responded to increased steroid therapy. Ten of the 21 CD grafts (48%) continue to function well at least a year post-transplant, despite many poor HLA matches.

**DISCUSSION AND CONCLUSIONS**

Fear of the possible consequences of protracted high-dose prednisolone therapy prompted the search for indicators of reversibility in acute rejection. Reversible episodes responded within five days in 94% of cases, and we used this information to diagnose irreversible rejection.

The present regime is to give up to three 1-g IV prednisolone doses per rejection episode, on alternate days, while measuring the serum creatinine and clearance daily, with frequent technetium blood-flow studies. This approach has apparently protected recipients while not impairing graft survival.

Examination of the complications encountered in recipients treated with single and repeated one- to three-gramme courses of prednisolone suggests that their frequency and severity are related to several interacting factors.

**Total dose and frequency**

*Urinary extravasation.* Bladder stress (overdistention, spasm) preceded formation of two fistulae. Urinary leakage invariably led to infection.

*Prior bacteriuria.* All five patients with Gram-negative wound infections or pyelonephritis and sepsis had prior bacteriuria or active infection.

*Severe renal dysfunction* when continued azathioprine and large steroid doses are
required. The concurrence of severe renal dysfunction, possibly related to increased azathioprine effects, and high-dose steroid strongly predisposes to infectious complications.

The continuation of azathioprine during post-transplant oliguria and dysfunction from rejection may be unavoidable. The use of repeated large steroid doses at such a time is particularly risky. Technetium renal blood-flow studies have been valuable in detecting resolution or rejection during post-transplant oliguria, justifying continued therapy.

Limitation of steroid exposure and guarding against predisposing factors can help protect recipients from morbid and fatal complications.

References

Hill, R G, Dahrling, B E, Starzl, T E and Rifkind, D (1967) American Journal of Medicine, 42, 327
Kincaid-Smith, P (1969) Lancet, ii, 920
Tenth Registry Report (1973) ACS/NIH Organ Transplant Registry
Williams, G M, White, H J O and Hume, D M (1967) Transplantation, 5, 837

Open Discussion

F BRUNNER (Basle) I’d like to know what biopsy criteria you use to remove a kidney.

SIEGEL When the biopsy shows haemorrhagic necrosis. Lack of response to immunosuppressives is an indication for biopsy, not graft removal, since a patient with apparently severe rejection may have ATN. We have also found a good correlation between isotope studies and biopsy findings.

BRUNNER Do you get a patchy distribution on the scan or is it the clearance that you’re looking at?

SIEGEL We plot changes in counts over the whole kidney, and find that rejection and actute tubular necrosis can be distinguished quite easily.