LESS AGGRESSIVE REJECTION THERAPY AND LOW-DOSE CORTICOSTEROIDS LEADING TO SATISFACTORY CADAVERIC KIDNEY GRAFT SURVIVAL AND LOW MORBIDITY RATE

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Summary

A less aggressive approach in treatment of rejection crises has been introduced since January 1979. Findings in 39 patients demonstrate that rejection treatment can be started later and be applied with considerably less frequency without an increase in graft loss.

A reduction of more than 50% in corticosteroid dosage applied within three months after transplantation seems to be possible, with a sharp decrease of morbidity rate.

Introduction

Since the beginning of the Leiden kidney transplantation programme in 1969, the basic corticosteroid scheme has not changed. The main characteristics of this scheme were a low maintenance dosage and an aggressive approach to a rejection crisis. The corticosteroid dosage was raised as soon as clinical evidence for a rejection crisis was presumed.

We changed this policy from January 1979 because data proving that the former approach gave superior graft survival was lacking. More clinical evidence was now required before beginning rejection treatment. The effect of this less aggressive rejection therapy is the subject of this article.

Patients and methods

In Leiden Medical Center kidney transplantations are performed under the auspices of Eurotranplant. The clinical course of adult transfused patients transplanted with a cadaveric renal allograft in the period from 1970 to January 1979 was studied and compared with the clinical course in patients transplanted after January 1979. HLA (A and B) typing was done prospectively and HLA DR typing partially retrospectively and partially prospectively. Only the clinical data of patients with a functioning graft after six months were studied for simplicity.
The study consisted of two separate analyses:

1. The number of rejection treatments given within six months after transplantation in both groups of patients were compared.

2. Detailed clinical data obtained during the first three months after transplantation of patients in 1977/78 were compared with those of patients transplanted in 1979. A change in surgical technique prevented any urinary leakage in patients transplanted in 1979. Therefore seven patients with urinary leakage transplanted in 1977–1978 were not included in this analysis.

**Therapy**

Antacids were given routinely. Since about 1977 cimetidine was given for certain indications.

Prophylactic antibiotics (chloramphenicol and cloxacillin) were given for 48 hours starting just before transplantation and every re-intervention.

**Immunosuppression**

During the first six days after transplantation prednisone was given in the following dosage sequence: 80, 60, 40, 35, 30, 25mg per day. For a rejection treatment the dosage was raised to 2–3mg/kg (generally 150mg) for five days. The dose was then lowered within 12–15 days to 0.5mg/kg. Prednisone was given in four doses per day. Dosages above 80mg per day were given i.v. and below 80mg orally.

After 1975 rejection episodes were occasionally treated by giving 15mg/kg solumedrol on three alternate days. Azathioprine was given as an additional immunosuppressive drug. The dosage depended on body weight, graft function and possible toxic effects.

Before 1979 this corticosteroid scheme was used as a guideline, but sometimes variations were used. It was decided in 1979 that this scheme was to be followed regularly. The dosage of corticosteroids was adjusted to body weight. When the rejection process did not respond satisfactorily the prednisone dosage was not raised again until the dosage had been tapered below 50mg per day.

Occasionally solumedrol (methylprednisolone) was added when the prednisone dosage was between 100mg and 50mg/day.

Diagnosis of a rejection crisis was made on the basis of clinical symptoms such as fever, eosinophilia, hypertension, proteinuria, decrease or no adequate increase of diuresis, increase or not adequate decrease of serum creatinine. When indicated biopsies were performed.

**Results**

In 1979 rejection treatments were given later than previously (Table I). Forty-eight percent of the patients transplanted in 1979 received the first treatment for rejection more than ten days after transplantation, compared with only seven percent of the patients transplanted before 1979. Rejection treatments were applied with less frequency within the first six months (Figure 1). In 1979, 63% of the patients received only one or no treatment for rejection compared with 14% in 1970–1979.
TABLE I. Start of first rejection treatment in patients with a functioning graft

<table>
<thead>
<tr>
<th>Days after transplantation</th>
<th>1970—1979 (n = 176)</th>
<th>1979 (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 — 5</td>
<td>59%</td>
<td>13%</td>
</tr>
<tr>
<td>6 — 10</td>
<td>34%</td>
<td>39%</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>7%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Figure 1. Distribution of the number of rejection treatments in patients with a functioning graft after six months.

The percentages of patients with three or more treatments were 7 and 53% respectively.

This less aggressive approach did not result in an increase in graft loss. Graft survival after six months was respectively 67% (1970—1979) and 82% (1979).

The improved results could not be directly attributed to a better HLA (A and B) and DR matching or a change in transfusion policy.

The conclusion from the first analysis is that a less aggressive approach did not adversely influence kidney graft survival after six months (graft survival after six months was 73% in 1977—1978 (n = 77) and 82% in 1979 (n = 39). Patient survival after six months was 95% in both periods.
TABLE II. Prednisone dosage and morbidity rate in patients with a functioning graft within three months after transplantation

<table>
<thead>
<tr>
<th></th>
<th>1977/78 (n = 49)</th>
<th>1979 (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>complications — severe</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>— mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of infections</td>
<td>63</td>
<td>15</td>
</tr>
<tr>
<td>% of patients without infections</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>Median length of first hospital admission</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td>Average dose of corticosteroids</td>
<td>7.8g</td>
<td>3.6g</td>
</tr>
</tbody>
</table>

The results of the second analysis are depicted in Table II. There was a considerable reduction in the amount of corticosteroids administered within three months, respectively 7.8g (1977–1978) versus 3.6g (1979). The number of complications decreased as well (e.g. the percentage of patients without an infection increased from 18% (1977–1978) to 57%. The median length of the first hospital admission decreased from 43 to 28 days as a consequence of the decrease in the number of rejection treatments and reduced morbidity rate.

Avascular necrosis of bone occurred in 30% of the patients transplanted before 1979. It appears that about 5,000mg of prednisone administered during the first three months is a critical dosage above which avascular necrosis may develop [1]. In 1979 only 10% of the patients received more than 5,000mg of prednisone. Therefore it seems reasonable to expect that the percentage of avascular necrosis will be considerably less in 1979 than previously.

Kidney function showed a slight tendency to decrease, although the differences were not significant. The mean creatinine clearance is ± 10ml per minute less in patients transplanted in 1979.

Discussion

Almost 20 years after the introduction of corticosteroids in clinical transplantation, the desirable level of corticosteroid therapy is still uncertain [2]. This suggests that transplantation research may not have chosen its priorities correctly [3]. Systematic study of corticosteroid therapy after kidney transplantation deserves high priority. One of the major clinical problems regarding corticosteroid therapy is whether our timing of rejection therapy is critical. Is it necessary to raise the corticosteroid dosage as soon as there are a few minor symptoms of a rejection crisis, or is it possible to wait for some time before starting therapy?

The answer to this question determines the therapeutic approach and the importance of immunological monitoring as a tool for detection of rejection. Our
results and those of others [4] suggest that no instant therapeutic action is needed when a rejection crisis is suspected.

Another conclusion from our data is that low dosage corticosteroids in the first period after transplantation gives satisfactory results in the short time with a low morbidity rate. High dosages do not seem to have a beneficial effect on graft survival and only serve to increase morbidity rate. Our findings are in complete agreement with those of McGeowan [5]. In the periods studied, no significant difference in HLA A and B and DR matching grade was noted. We cannot exclude the possibility that excellent HLA (A and B) matches made it possible to reduce prednisone dosage.

This suggestion is in agreement with our findings that the amount of prednisone necessary to suppress a rejection crisis is dependent on the degree of histocompatibility.

Corticosteroids influence the immune reaction at various levels: as well as suppression, an enhancement of immune reactions is observed [2]. It is to be expected that better knowledge concerning the complicated role of corticosteroids on the immune system will lead to a considerable decrease in the amount of corticosteroid thought necessary to suppress a rejection crisis.

Acknowledgments

We thank Mrs L H van Welij and Mrs M J Mentink for typing the manuscript and Mrs Y E A van Hooff-Eijkenboom for her help in compiling the data.

References

2 Fauci AS. J Reticuloendothel Soc 1979; 26 suppl: 727
3 Van Hooff JP. Letter to the Editor, Lancet 1980; 2: 43

Open Discussion

JEEKEL (Rotterdam) You lowered your dose of corticosteroids and have less morbidity but in order to do that you must have changed your criteria for diagnosing rejection reaction. How did you change your criteria?

VAN-HOUFF There is time for checking and double checking the clinical impression. This has been the major change in our philosophy. The previous policy was that as soon as there was some indication, such as temperature, hypertension, eosinophilia, no adequate increase in urinary output, no adequate decrease of serum creatinine, a rejection crisis was suspected and prednisone dosage was raised. Clear cut experimental data proving that this approach is necessary is lacking. At the moment we wait until a classical clinical picture of rejection develops.