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ARE THERE NON-STEROID-DEPENDENT REJECTION EPISODES?

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Introduction

Two different mechanisms leading to graft rejection are generally described.

The first involves the presence of antibodies directed against the graft antigens and is responsible for vascular lesions.

The second, of cellular origin, results in cellular infiltration of the kidney and
subsequently the occurrence of fibrosis.

However, in recent years evidence has accumulated that vascular changes are common in many, if not all, renal allografts and that once the vascular walls are damaged an inflammatory reaction may develop in the interstitium of the kidney [1]. This reaction is due to increased vascular wall permeability and is either localised around the vessel or is more diffuse. If lesions are not severe enough to induce vascular thrombosis, the clinical appearance will be that of acute renal failure because of the decreased renal blood flow secondary to increased vascular resistance. The interstitial reaction to vascular wall damage probably acts as an amplifier of rejection by increasing the parenchymal resistance, thus resulting in a new drop in renal blood flow.

In mild cases without vascular thrombosis, even in the absence of therapy, swelling of endothelial cells will improve and the renal blood flow will increase, as will renal function, but interstitial lesions will progress to fibrosis.

All these facts have been proven by clinical observations and it is possible to observe spontaneous remission of both renal failure episodes and vascular lesions.

More than twenty years ago, in 1959, in our first description of the rejection crisis [2], we showed that the transplant recovered good function despite the fact that the recipient received no treatment.

However, steroids were introduced for the treatment of acute rejection [3], and most acute rejection episodes respond to such treatment, but we have shown with others [4] that routine administration of steroids cannot prevent acute rejection episodes and that the percentage of reversible or irreversible renal failure episodes, as well as the percentage of kidneys functioning at six months, did not differ whether recipients were pre-treated by steroids or not. We therefore concluded that steroids are probably a poor immunosuppressive agent but a very good anti-inflammatory drug. Unfortunately, steroids are responsible for most of the severe complications observed after transplantation.

For this reason, we initiated two studies in an effort to reduce the steroid dosage given to patients and even to replace steroids by non-steroid anti-inflammatory drugs.

**ACTION OF ATG ON THE INCIDENCE OF REJECTION EPISODES AND ON DOSES OF STEROIDS RECEIVED BY PATIENTS**

Between March 1977 and August 1978, we participated in an international multicentre study aimed at determining the actual effectiveness of ATG in prolonging kidney graft survival [5].

**Material and methods**

Fifty consecutive cadaver kidney recipients were randomly assigned to a treatment or a control group. In both groups patients received the same standard immunosuppressive regimen of prednisolone and azathioprine.

In the treated group ATG was administered intravenously every day for two weeks, then every other day for another two weeks; 40mg of intravenous methyl-
prednisolone sodium succinate (included in the total daily prednisolone dose) were given prior to each ATG infusion. Daily ATG doses were determined by the level of rosette forming cells, with the goal of maintaining this level at 10% of baseline values. Sex, age, total ischaemia time of the graft, HLA compatibility, previous pre-immunisation and blood transfusion status of patients were comparable in the treated and the control groups.

Results

In the treated group we observed (Table II) a statistically significant decrease in the incidence of rejection episodes, a significantly prolonged kidney survival up to two years, a better level of kidney function during the first post-transplantation month and smaller mean daily doses of steroids received by patients during the first three months. We concluded that the lot of ATG used in the study was both effective and innocuous.

TABLE II. Incidence of 'rejection' episodes, doses of steroid and kidney survival in control and experimental groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of patients</th>
<th>1st month reversible rejection</th>
<th>F*</th>
<th>Dose of steroids (mg/kg/day) during the first 2 months after transplantation</th>
<th>Two year post transplantation kidney survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25</td>
<td>16</td>
<td>0.64</td>
<td>2.84 ± 0.26</td>
<td>52%</td>
</tr>
<tr>
<td>ATG</td>
<td>24</td>
<td>7</td>
<td>0.29</td>
<td>1.87 ± 0.18</td>
<td>79%</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td>&lt; 0.02</td>
<td>&lt; 0.005</td>
<td>&lt; 0.02</td>
</tr>
</tbody>
</table>

*F: frequency per patient

REPLACEMENT OF STEROIDS BY NON-STEROID ANTI-INFLAMMATORY DRUGS

The above results led us to undertake a pilot trial to determine whether this very powerful immunosuppressive action of ATG might allow replacement of steroids by non-steroid anti-inflammatory drugs without the harmful immunological effects of these inhibitors of prostaglandin synthesis [6].

Material and methods

Fifteen mismatched, non-responder cadaver kidney recipients were prospectively randomised into two control groups, 1 and 2, and an experimental group 3.

In control group 1, patients were treated by our usual protocol, 3mg/kg/day azathioprine and 5mg/kg/day steroids for 5 days, which is gradually reduced to reach 0.25mg/kg/day at day 75.
In control group 2, patients were treated by the same protocol plus ATG at a dose of 11mg/kg/day for 15 days and then the same dose on alternate days for 3 months.

In the experimental group 3, patients were treated by the same dose of azathioprine and of ATG as in experimental group 2. They received no steroids but instead a non-steroid anti-inflammatory drug (Ibuprofen) at a dose of 27mg/kg/day for 5 days, gradually tapered to 15mg/kg/day at day 75.

Results (Table III)

In the experimental group, one patient had a non-reversible rejection episode despite recourse to steroid therapy, two patients had spontaneously non-reversible rejection episodes which resolved after steroid therapy and two patients never received steroid therapy and are doing well 7 and 3 months after transplantation.

TABLE III. Comparison of incidence of rejection episodes among control and experimental group

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Death</th>
<th>Irreversible rejection</th>
<th>No. of reversible rejection episodes Steroid treated</th>
<th>No. of reversible rejection episodes Not treated</th>
<th>No rejection episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group I</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Control group II</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Experimental group</td>
<td>6</td>
<td>1*</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* Death during surgery

Although it is impossible to draw definite conclusions based on this limited and recent pilot trial, it does seem clear that there are a few early acute renal failure episodes, probably of immunological origin, which can improve spontaneously in the absence of steroid therapy. It does not seem utopic to hope that the association of a powerful immunosuppressive drug with a harmless anti-inflammatory agent may permit a decreased incidence of rejection episodes without recourse to steroid therapy.

Summary

We undertook two randomised studies in an effort to decrease the dosage of steroids in transplanted patients and to replace harmful steroid therapy by non-steroid anti-inflammatory (NSAI) drugs.

In the first study, 50 consecutive transplant recipients were randomly assigned to the treatment or the control group. In both groups, patients received azathio-
prine and prednisolone. ATG was added to this protocol in the experimental group. The number of renal failure episodes and consequently the amount of steroid necessary to control these episodes were significantly lower in the ATG group than in the other group. Two year post-transplantation kidney survival was 79% in the ATG group and 52% in the control group.

In the second study, 15 consecutive transplant recipients were randomly assigned to two control groups and to one experimental group, where steroids were replaced by NSAI drugs. This preliminary, and very limited, pilot trial demonstrates the existence of early acute renal failure episodes, probably of immunological origin, which can improve spontaneously in the absence of steroid therapy.

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STEROIDS AND REJECTION TREATMENT IN THE GOTHENBURG TRANSPLANT PROGRAMME

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Introduction

The kidney transplant programme in Gothenburg started 15 years ago in 1965 on a modest scale during the first years, after which the frequency increased and from 1972 onwards approximately 100 kidneys per year have been transplanted. Up to now more than 1100 transplantations have been performed in 800 patients. Over 80% of the grafts have been of cadaveric origin.

Kidney transplantation has been the method of choice for the treatment of patients with terminal uraemia in our region which has resulted in only a minority of uraemic patients being taken care of by chronic dialysis. The transplantation frequency during the last 7 years has corresponded to 25 transplantations per million population per year. The acceptance of patients for transplantation has

*Unfortunately Professor Gelin was prevented by illness from taking part in this Symposium and we have since learned with sorrow of his untimely death (see Preface). Eds