Original Article

Elective Conversion from Cyclosporin to Azathioprine in Living Related Donor Kidney Transplants

M. A. Sobh, A. B. Shehab Eldein, F. E. Moustafa and Mohamed A. Ghoneim
Urology and Nephrology Centre, Mansoura University, Egypt

Abstract. Thirty-five patients with living related donor kidney transplants who were initially immunosuppressed with cyclosporin and a small dose of prednisolone were electively converted to receive azathioprine. Conversion was carried out 6 months after initiation of cyclosporin therapy. Cyclosporin was initially given as part of a random study in 13 cases (group I), and due to the presence of immunological high-risk factor(s) or to control steroid-resistant rejection episodes in 22 cases (group II).

In group I, three cases developed acute rejection symptoms which were easily controlled. In group II, conversion was followed by acute rejection episodes in six patients. In two cases these were easily controlled. In four cases the episodes were unsuccessfully controlled, even after reintroduction of cyclosporin.

We conclude that conversion from cyclosporin to azathioprine in living related donor kidney transplant patients at 6 months is a safe and beneficial practice in immunologically stable cases, but hazardous in those with high-risk immunological factors.

Key words: Azathioprine; Conversion; Cyclosporin; High-risk patients; Living related donor kidney recipients; Rejection

Introduction

The long-term sequelae of cyclosporin nephrotoxicity are not yet known but there is considerable anxiety that it may lead to chronic and irreversible renal damage [1]. Furthermore, the financial burden created by the long-term use of this expensive drug has stimulated some centres to convert patients, treated initially by cyclosporin, to the conventional immunosuppressive regimens using azathioprine. All the publications to date have described conversion in cadaveric kidney transplantation patients [2-5].

We report our experience in elective conversion from cyclosporin to azathioprine in living related donor kidney transplantation.

Materials and Methods

Thirty-five patients, 26 male and 9 female with ages ranging between 9 and 46 years were the subject of this study. Table 1 shows the status of these patients prior to conversion.

All the patients received third-party blood transfusion prior to transplantation, none of them received donor-specific blood transfusion. Cyclosporin was given in a dose of 5 mg/kg per day parenterally in the first 2 postoperative days, then in a dose of 12 mg/kg per day orally during the 1st month, 10 mg/kg per day during the 2nd month, 8 mg/kg per day during the 3rd month, and a maintenance dose of 6 mg/kg per day up to the time of conversion. These doses were readjusted to give whole blood cyclosporine trough levels around 800 ng/ml during the 1st month, 600 ng/ml during the 2nd month, 400 ng/ml during the 3rd month and a maintenance level around 300 ng/ml. Prednisolone was given in a dose of 100 mg on the operative day and rapidly tapered to reach an oral dose of 20 mg/day within 2 weeks.

Conversion was implemented 6 months after the initiation of cyclosporin therapy. At conversion, azathioprine was given in an oral dose of 2-3 mg/kg per day and...
Conversion from Cyclosporin to Azathioprine

cyclosporin was gradually withdrawn and completely stopped within 1 week. Patients were maintained on the same dose of prednisolone. Cyclophosphamide was given in a dose of 2–3mg/kg per day instead of azathioprine when there was rise in serum bilirubin. Patient were followed up for a period ranging between 6 months and 24 months after conversion (mean period 14 months).

Besides the routine clinical, laboratory and radiological follow-up, the patients were subjected to frequent fine needle aspiration cytology (FNAC) of their grafts for early diagnosis of graft rejection. Percutaneous needle biopsy was performed whenever rejection episodes were suspected.

Table 1. Patients subjected to elective conversion from cyclosporin to azathioprine therapy

<table>
<thead>
<tr>
<th>No.</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>CsA was given as a part of random study to compare CsA and a small dose of steroid with conversion at 6 months vs conventional immunosuppression</td>
</tr>
<tr>
<td>10</td>
<td>Patients with high risk factors: two-haplotype mismatch, high MLC, history of positive direct cross-match, different but compatible blood groups of donor and recipient, and retransplants</td>
</tr>
<tr>
<td>12</td>
<td>Cyclosporin given to control steroid-resistant rejection episodes</td>
</tr>
</tbody>
</table>

Results

Following conversion there was an improvement in the graft function in 18 out of the 35 cases. The mean serum creatinine was $1.8 \pm 0.3$ mg/dl before conversion and $0.7 \pm 0.2$ mg/dl afterwards. The improvement started few days after the reduction of cyclosporin. The remaining 17 cases continued with the same graft function.

Out of 16 hypertensive patients, the use of hypotensive drugs became unnecessary in five and a dose reduction was possible in four. Seven patients with steroid-induced diabetes, the hypoglycaemic agents were withdrawn in one patient and decreased in another three. It was also observed that three patients regained normal liver function after conversion from cyclosporin to cyclophosphamide.

After conversion, ten acute rejection episodes were reported in nine cases. Four of these rejection episodes occurred 3–4 weeks after conversion, three at 2–3 months, and two at the end of the 6th month. All these rejections were tubulointerstitial except one which was vascular in nature.

Table 2 shows the frequency and the outcome of the rejection episodes following conversion. Three patients were from the first group. Two of these three cases were easily controlled by methylprednisolone. Cyclosporin had to be reintroduced for the third case. Six cases were from the second group. In only two cases, the acute rejection was contained, yet four grafts were lost despite reintroduction of cyclosporin. The difference between the two groups was found to be statistically insignificant ($P > 0.05$).

Table 2. Frequency and outcome of acute rejections after elective conversion

<table>
<thead>
<tr>
<th>Group</th>
<th>Frequency</th>
<th>Reversibility</th>
<th>$\chi^2$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3/13</td>
<td>3/3</td>
<td>0.0753</td>
<td>0.787</td>
</tr>
<tr>
<td>II</td>
<td>6/22</td>
<td>2/6</td>
<td>3.6000</td>
<td>0.0578</td>
</tr>
</tbody>
</table>

Discussion

The first trial encouraging conversion was reported by an Oxford group [3]. Elective conversion at 90 days was carried out for 30 patients. Irreversible rejection occurred in only one patient whose graft function was satisfactory prior to conversion. Similar good results were reported from the Netherland by Tegzess and his co-workers [5], conversion being carried out in 21 cadaveric kidney transplant patients before the 4th postoperative month. No kidneys were lost during the observation period of 9–14 months.

On the other hand, less favourable results were reported by Land et al [2] and Adu et al [4]. Land et al in a randomised study performed conversion at 3 months after transplantation. Three of nine converted cases lost their grafts through irreversible rejection. Furthermore three of eight patients lost their kidney when conversion was performed to control nephrotoxicity. The results reported by Adu et al were similarly disappointing. Of the five patients who underwent conversion, one died from lung infection and three developed acute rejection episodes.

In view of these conflicting data and due to the lack of information regarding conversion in the living related donor situation, this study was initiated. We have opted to start the conversion at the sixth month after initiation of cyclosporin therapy. In addition, cyclosporin was withdrawn gradually over a period of 1 week, during which it was substituted by azathioprine in a dose of 3 mg/kg per day. It was presumed that these two factors may decrease graft rejection after conversion.

Following conversion, nine of the 35 patients suffered from acute rejection episodes. Of these nine cases, three
were from group I and six were from group II. All cases from group I were easily reversed. On the other hand, the control of rejection among patients from group II was only successful in two patients (30%). The onset of rejection varied from 4 weeks to 6 months following conversion. This observation emphasises the necessity of close follow-up of these patients for a longer period of time. In the final analysis, it seems legitimate to carry out conversion protocols in living related donor kidney transplants among stable cases with low immunological risk factors. In addition to the economic saving the patients do benefit from an improvement in renal function, possible improvement in their diabetic status, and easier control of their hypertension. Similar observations had been reported by others in cadaveric settings [5-8]. On the other hand, and on the basis of our data, the risks of graft loss are too high if conversion is attempted among immunologically high-risk patients, or in patients for whom cyclosporin was given to combat steroid-resistant rejection episodes.

Acknowledgements. We wish to thank Miss Nehad Abdel Malik and Miss Mervat Lotfy for their excellent technical help and Mrs Angel Yanni and Mrs Marwa Tabrizy for their accomplished secretarial work.

References