IMPROVEMENT IN CYCLOSPORINE HANDLING BY ANTI-LYMPHOCYTE GLOBULIN IN THE EARLY POST-OPERATIVE PERIOD

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Summary

The value of prophylactic anti-lymphocyte globulin (ALG) treatment after transplantation was examined in a prospectively randomised study. The control group was treated with azathioprine and steroids only. In a third group prophylactic ALG combined with azathioprine and steroids was given for 8.7±2.25 days after transplantation and was then replaced by cyclosporine and steroids. Renal graft survival rates could be improved if the conventional immunosuppression was accompanied by ALG prophylaxis. However, additional cyclosporine treatment proved to be desirable since in this way the number of early acute rejection episodes could be further reduced.

Introduction

Although the benefits of prophylactic ALG administration immediately after transplantation have been reported repeatedly [1], this method of treatment nevertheless has not been generally accepted [2]. Therefore in the prospective study presented here the following questions were examined:

1. How does the transplant survival rate under prophylactic ALG treatment compare with conventional immunosuppressive therapy with azathioprine and steroids alone?

2. Which side effects of ALG treatment may be expected and how can they be reduced?

3. Can the immediate kidney function after transplantation be improved by ALG prophylaxis?

4. Is it advisable to change over from conventional immunosuppression combined with ALG prophylaxis to cyclosporine in the further course of treatment?
Material and methods

All patients presenting between May 1981 and July 1983 for a first cadaver kidney transplant entered a prospectively randomised trial (groups A and B).

In group A (n=47) patients received 5ml/10kg body weight (30ml maximum) of ALG (Mérieux®) per day during the first three weeks after transplantation. Additionally conventional immunosuppression with azathioprine and steroids was given as in the control group. The daily dose of ALG was administered over 24 hours via a central venous catheter with the aid of a pump.

In group B (control group) (n=47) immunosuppression consisted of azathioprine and steroids only. The steroid therapy was identical in both groups: all patients received 250mg of prednisolone the first day after transplantation. This dose was daily reduced by 25mg to 100mg prednisolone and then by 5mg every second day to 10mg prednisolone. In the case of a rejection episode the patients received additional pulse therapy with methylprednisolone (maximum 5 grams).

The dose of azathioprine depended on the body weight (maximum 3mg/kg body weight/day), and on the leucocyte and platelet counts.

Group C (n=35) contains all first cadaver kidney transplants which were performed from September 1983 to July 1984. The patients in this group received ALG in combination with conventional immunosuppression (as in group A) for a minimum of seven, but maximum of 14 days after transplantation. Subsequently, ALG and azathioprine were withdrawn and were replaced by cyclosporine which was given in a dose of 10mg/kg body weight/day (a serum cyclosporine level of 300 to 500ng/ml was aimed at). The steroid therapy was the same as in groups A and B.

Results

There were no significant differences between the three groups as regards the patients’ ages and pre-transplant periods, the HLA and DR-matching or the preservation time of the grafts.

Graft survival rate (groups A and B)

At one year the graft survival rate in the ALG prophylaxis group was 33/47 (70.2%) (group A) as compared with 28/47 (59.6%) in group B. The three month graft survival rates are given in Figure 1.

The graft survival rate in group C after one month was 33/35 (94.3%) and after three months 29/32 (90.6%) (Figure 1).

Patient survival

Groups A and B did not differ significantly as regards the hospital mortality rate: in the ALG group two patients died post-operatively from pneumonia, and in the control group two patients also died (one due to pneumonia and the other from wound sepsis).

There were three late deaths in the ALG group (group A): one patient died
because of liver failure, another one because of a perforated sigmoid diverticulitis and one patient from a miliary tuberculosis. The one year patient survival rate, therefore, was 89.4 per cent in group A and 95.8 per cent in group B.

No patient in group C died in the first four weeks after transplantation or later on.

**Primary kidney function after transplantation**

Eighty per cent of all kidneys in group A, but only 24.4 per cent in group B (p<0.05) started to function after transplantation in such a way that dialysis was not necessary from the second week after transplantation. In group C 88.6 per cent of all kidneys were functioning well in the second post-operative week.

**Acute rejection episodes**

The percentage of patients that suffered an acute rejection episode in the first three weeks after transplantation is given in Figure 1. More rejection episodes were found in group B than in group C.

**Amount of steroids administered**

The three groups differed significantly as regards the amount of steroids administered during the first three weeks after transplantation. Patients in group A
received a mean of 3731.9±1781.1mg, patients in group B 4912.3±2243.7mg, and those in group C 2691.0±708.9mg of steroids (p<0.05).

**Special ALG problems (group A)**

The mean period of administration of ALG was 18.8±3.6 days, since it was only possible in 34/47 (72%) of all patients to give ALG as planned for the whole period of 21 days. The treatment had to be stopped prematurely for the following reasons: leuco- or thrombocytopenia in five patients, catheter sepsis in one patient, ALG intolerance in two patients, pneumonia in one patient, graft removal in three patients, and death in one patient.

Patients who received the complete ALG prophylaxis showed a significantly better one year graft survival rate as compared to the remaining patients of this group (87.9% vs 44.4%, p<0.005).

**Discussion**

The results presented here demonstrate that renal graft survival rates can be improved if conventional immunosuppression (with steroids and azathioprine) is accompanied by ALG prophylaxis in the first weeks after transplantation. This is due to the fact that early rejection episodes can be successfully prevented by these means. This initial positive effect is also of advantage later on, since in the later course rejection episodes occurred in both groups (ALG and control group) with the same frequency.

In spite of this favourable result, however, we suggest a modification of the treatment protocol to avoid the increased risk of infection with the use of ALG. To reduce the side-effects, ALG should be given for shorter periods as planned here. In future, therefore, we will administer ALG for not more than 14 days after transplantation, since after this time the rate of complications increased considerably.

A further essential finding of this study consists of the observation that immediate kidney function after transplantation could be improved significantly if ALG was given. The improvement in post-transplant renal function, under identical donor conditions and intra- and post-operative fluid therapy [3], can only be attributed to the fact that rejection episodes which were not discovered because of missing clinical signs and, therefore be misinterpreted as acute tubular necroses, are treated in time by the ALG prophylaxis, resulting in a lower rate of post-transplant dialyses.

The benefits of prophylactic ALG treatment, therefore, are based on the suppression of early rejection episodes (Figure 1), whereas later rejection episodes were not affected. Since these reactions must be prevented to obtain further improvement in results, the ALG prophylaxis was combined with a subsequent cyclosporine therapy in group C. In so doing we have chiefly administered cyclosporine in those cases in which the kidney had already started to function, and to avoid the difficulties which occur in anuric kidneys with cyclosporine because of its nephrotoxicity [4,5]. Although the optimal timing for changing
over from conventional therapy to cyclosporine has not been clearly defined, we think that it must lie between the 7th and 14th post-operative day, because on the one hand most of the kidneys have started to function satisfactorily up to this moment and on the other hand only slight side effects are to be expected from a short-term ALG prophylaxis.

Our experience with the new protocol is limited, however. The initial results demonstrate the advantage of changing over from ALG to cyclosporine: the number of rejection episodes observed in the first three weeks after transplantation was significantly reduced in group C as compared to the other groups, and consequently smaller doses of steroids were given. This led to a decreased risk of infection resulting in improved patient survival.

References

2 Groth CG. Transplant Proc 1981; 13: 460
3 Carlier M, Squifflet JP, Pirson Y et al. Transplantation 1982; 34: 201

Open Discussion

BRYNGER (Chairman) Thank you very much for this thorough representation of another way to use cyclosporine in combination. I think we, for the moment, are receiving information from different centres using a number of combinations and which one will be thought to be the optimum I think remains to be proven, but still your data are impressive. Are there any questions or comments.

PICHLMAYR (Hannover) I think it is very important to study some protocols of combining cyclosporine and ALG or azathioprine and this is true for your paper and for the paper presented before, but I am a little bit worried that we could be producing over-immunosuppression with these combinations. We have to remember the Stanford* experience where combining many things gave a very high incidence of tumours and so one should know a little bit more about the dosage and the blood levels of your cyclosporine treatment. If we combine drugs we have to very much reduce the dosage of the individual therapies.

GRUNDMANN That is right.