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The effect of the applied induction immunosuppressive therapy protocol on the allografted kidney condition

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Aim: *To assess the Eculizumab effect on the allografted kidney function in the immediate and early postoperative period.*

Materials and methods: *In kidney transplantation, 33 patients received Eculizumab in combination with Alemtuzumab (group 1). Other 38 patients (group 2) were enrolled for a comparative analysis. They received their induction immunosuppressive therapy with Alemtuzumab and plasmapheresis sessions. The following parameters were used for analysis: the urine output in the first 24 hours after surgery, the period of creatinine level drop to 3 mg/dL, a 24-hour protein excretion at day 30 after surgery, a glomerular filtration rate at day 30 after transplantation, histology of kidney allograft biopsy at 1 month post surgery.*

Results: *A comparative analysis has demonstrated much lower values of 24 hour proteinuria in group 1 than in group 2. As to the glomerular filtration rate, it was 1.9 times higher in group 1 than in group 2. The period of blood creatinine subnormalization was significantly shorter in group 1.*

The differences were statistically significant in all studied parameters (p=0.002–0.003).

Conclusion: *The allografted kidney function was much better in group 1 than in group 2. Thus, the combination of Eculizumab + Alemtuzumab had a more favorable effect on the function and morphology of allografted kidneys in the immediate and early postoperative periods compared to that of Alemtuzumab + plasmapheresis combination.*

Keywords: kidney transplantation, induction immunosuppression, Eculizumab, Alemtuzumab, allografted kidney function

Introduction

The purpose of the induction immunosuppressive therapy (IIST) is to prevent the risk of rejection. IIST in kidney transplantation is an intensive immunosuppression administered during the first days after the kidney transplantation. The drugs used to perform IIST included corticosteroids, monoclonal and polyclonal antibodies, kallikrein inhibitors, interleukin 2 antagonists, anti-lymphocyte globulins and others. [1-7]. Eculizumab (Soliris), the drug appeared in the pharmaceutical market, inhibits the effector function of the complement system and represents a breakthrough in the medical treatment of paroxysmal nocturnal hemoglobinuria, or atypical hemolytic-uremic syndrome (HUS).

In December 2012, we surprisingly found a potent effect of Eculizumab on reperfusion injury after we had administered the drug to a 1.5-year-old boy in the Operating Room during cadaveric kidney transplantation suspecting a hyperacute rejection. Solid-phase immune assays excluded our suspicions of the hyperacute rejection, but a rapid

recovery of the graft left no doubt about the effect of Eculizumab on reperfusion injury [8].

In the period from 1998 to 2013 we used plasmapheresis to control reperfusion injury [9]. After the case mentioned above, we sought to maximize the use of Eculizumab instead of plasmapheresis.

A further argument in favor of Eculizumab is no need to compensate for the loss of other induction drugs removed with plasma during plasmapheresis sessions, specifically Alemtuzumab, that had to be administered at a rate of 180 mg/hr during plasmapheresis.

In the available Russian and foreign medical literature, we found only scarce publications that described single cases of renal transplantation in patients with atypical HUS. We found no reports that would have given the analysis of clinical data. This is likely because of an extremely high cost of the drug. In this regard, we have reviewed our own experience in this field and present it in this paper.

Clinical Material and Methods

We compared two IIST protocols: Alemtuzumab + plasmapheresis without compensation (Group 2, the comparison group) and Eculizumab + Alemtuzumab (Group 1, the study group). The aim of the study was to investigate the effect of the used IIST Protocol on the function of the transplanted kidney in the immediate and early postoperative periods. We started using the Alemtuzumab and Eculizumab combination in January 2013. We have treated total 33 patients since then. The age of patients ranged from 2 to 19 years old (7.76 ± 5.01). There were 13 boys and 20 girls. The kidneys were transplanted from living related donors to 19 patients, and from cadaveric donors to 14 patients.

The causes of chronic kidney disease (CKD) in the patients of this group are shown in Table. 1.

Table 1. The causes of chronic kidney disease (CKD) in patients of Group 1

Diagnosis	Number of patients	%
Hypoplasia + Renal dysplasia	11	33.34
Nephrotic syndrome	6	18.18
HUS	4	12.12
VUR	4	12.12
Multicystic kidney disease	3	9.09
Fanconi's nephronophthisis	1	3.03
Denys-Drash syndrome	1	3.03
Chronic pyelonephritis	1	3.03
Right megaureter, CKD	1	3.03
Chronic glomerulonephritis	1	3.03
TOTAL	33	100

Note: VUR: vesicoureteral reflux.

The total dose of administered Eculizumab varied from 300 mg to 1200 mg depending on the body surface area. It was calculated using the formula: 700 x body surface area (m^2). In living related transplantations, Eculizumab was administered at 2-3 weeks prior to transplantation (the first dose), then the day of surgery prior to perfusion (the second dose), at day 4 after transplantation (the third dose). In cadaveric transplants, Eculizumab first administration was performed before the start of reperfusion, the second dosing was at day 4 after transplantation.

As for Alemtuzumab, the first dosing of the drug took place at 2-3 weeks prior to surgery, and the second dosing was performed on the day of surgery before the start of reperfusion. Sometimes the third dose was administered on the 4-th day after kidney transplantation. In patients of Group 1, Alemtuzumab was administered subcutaneously in a dose of 1 mg/kg, but no more than 30 mg. In cadaveric transplants, Alemtuzumab was first administered prior to reperfusion start, the second dose was administered on the 4-th day after surgery.

Group 2 included 38 patients aged from 3 to 60 years old (21.11 ± 16.44). There were 24 children, and 14 adults, including 24 males, and 14 females. Kidneys were transplanted from living related donors to 22 patients, from cadaveric donors to 16 patients. The causes of renal failure are shown in Table. 2.

Table 2. The causes of end-stage chronic kidney disease (CKD) in patients of Group 2

Diagnosis	Number of patients	%
Chronic glomerulonephritis	10	26.35
Hypoplasia + dysplasia	8	21,05
VUR	7	18.82
Multicystic kidney disease	6	15.38
HUS	3	7.88
Diabetes mellitus	2	5.26
Focal segmental glomerulosclerosis	1	2.63
Alport syndrome	1	2.63
TOTAL	38	100

In patients of Group 2, Alemtuzumab was administered subcutaneously in a dose of 1 mg/kg, but no more than 30 mg total. In live-related transplantations, the first dose of Alemtuzumab was administered at 2-3 weeks before surgery, the second dosing was performed on the day of surgery prior the start of reperfusion, and the third dose was administered on the 4-th day after transplantation. In renal transplants from cadaver donors, Alemtuzumab was first administered at 180 mg/hr on the day of surgery prior to the start of reperfusion.

The following parameters were used for comparative analysis: 1) a recipient's age; 2) the time of reduction in serum creatinine level to 3 mg%; 3) the urine output in the first 24 hours after surgery; 4) the number of HLA mismatches; 5) Kaplan–Meier probability estimates of the patient and graft survival; 6) the assessed daily proteinuria at postoperative day 30; 7) the glomerular filtration rate; 8) the number of rejection episodes; 9) the number of infection episodes; 10) the morphology of kidney allograft biopsy (KAB).

A comparative analysis was performed using the Mann-Whitney test.

Results

Since it was important to assess the effect of IIST protocol on the allografted kidney function, a special attention was given to the following parameters: the time of reduction in serum creatinine level to 3 mg%, the glomerular filtration rate at 30 days after surgery; the daily urinary protein excretion. The results are shown in Table. 3.

Table 3. Changes in the parameters of the allograft function over time considering the protocol used for induction immunosuppression

Parameter	Group 1	P value	Group 2
The time of reduction in serum creatinine level to about 3 mg% (postoperative day)	± 0.7 ± 1.07	<0.005	± 4.89 ± 8.82
Glomerular filtration rate on day 30 after surgery	± 90.97 ± 36.11	<0.005	± 48.16 ± 35.80
The daily urinary protein excretion on day 30 after surgery	± 0.12 ± 0.15	<0.002	± 0.51 ± 0.65

The difference was statistically significant for the following parameters: the day of reduction in serum creatinine level to about 3 mg%; the follow-up period; daily proteinuria on the 30-th postoperative day; a glomerular filtration rate. In Group 1, serum creatinine returned to normal value much earlier, and the glomerular filtration rate was significantly higher. The daily protein excretion in patients of Group 1 was significantly lower than in Group 2. The calculated Kaplan–Meier probability estimates of patient and graft survival were nearly similar in both groups ($p = 0.21$).

The comparison of allograft needle biopsy findings showed that statistically significant differences between the groups were observed only in CV parameter that characterizes the state of the vessels in the biopsy sample. The comparison of studied morphology demonstrated the numerical value of this parameter being equal to zero in Group 1 and 0.18 ± 0.43 in Group 2 (Table. 4).

Table 4. Allografted kidney biopsy results compared between the groups in CV parameter

	Group 1	p value	Group 2
CV	0	0.020	0.18 ± 0.43
Period after surgery (days)	30 ± 5	> 0.5	30 ± 5

The KAB morphology in other parameters was almost similar in the groups. No drug-related side effects were seen in any of the groups.

Discussion

From the start of implementing the kidney transplantation in clinical practice we performed IIST using the bolus administration of corticosteroids in a dose from 500 to 1000 mg. Then, the new immunosuppressive drugs appearing in the market replaced corticosteroids.

Campath (Alemtuzumab) and Eculizumab (Soliris) are the most recent novel drugs developed for immunosuppression. Since our start of using Eculizumab, we have been interested in finding the answer to the question: what effect this drug produces on the function of the allografted kidney in the immediate and early postoperative period. To answer the question we conducted the study. The available number of patients in both groups gave us the opportunity to make a comparative statistical analysis.

Conclusion

In summary, the conducted comparative study has shown a better allografted kidney function in Group 1. Therefore, the Alemtuzumab and Eculizumab combination has a more beneficial effect on the function and

morphology of the allografted kidney in the immediate and early postoperative periods compared to the Alemtuzumab and plasmapheresis combination.

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