V.A. Goryainov, M.M. Kaabak, N.N. Babenko, M.M. Morozova, E.N. Platova, L.I. Agureeva, V.V. Panin, O.V. Dymova
Petrovskiy Russian scientific center of surgery, Moscow, Russian Federation

Use of tacrolimus in children for transplantation of kidneys taken from live relative donors

Author affiliation:
Goryainov Viktor Andreevich, leading research scientist at the kidney transplantation department of the Petrovskiy Russian scientific center of surgery

Address: 2, Abrikosovskii ln., Moscow, 119435; **tel.:** +7 (499) 248-13-44; **e-mail:** vik-kid@mail.ru

Article received: 22.01.2014. **Accepted for publication:** 14.05.2014.

The authors present their experience of immunosuppressive therapy with calcineurin blockers in the post-transplantation period (after living-related kidney transplantation). ***The study was aimed at*** *determining effect of immunosuppressive drug tacrolimus on results of living-related kidney transplantation in children (group 1). The 58 children, who did not receive tacrolimus in the process of the study, constituted the control group (group 2). The following parameters were used to perform comparative analysis: Kaplan-Meier cumulative survivability of recipients and transplants, Cox cumulative hazard level, log-rank test. Moreover, we calculated the rates of transplanted kidney loss and mortality.* ***Results:*** *survivability of transplants and patients was higher in the main group than in the control group ($p < 0.05$).* ***Conclusions:*** *thus, results of the performed analysis allow claiming that use of tacrolimus for immunosuppressive therapy positively affects results of the living-related kidney allotransplantation in children.*
Keywords: *allotransplantation, survivability, transplant, immunosuppression, efficacy, children.*

INTRODUCTION

Appearance of a new pharmaceutical in the international market always raises a question whether it may be applied in children. Immunosuppressive inhibitor drug calcineurin tacrolimus (original trade names – Prograf and Advagraf; Astellas, Japan) established in 1988 is no exception [1-5]. There are considerably fewer publications on the use of the immunosuppressant after organ transplantation in children, though, and they are usually dedicated to the tactics of shifting from the original drug to a different drug [4] and alteration of active substance concentration in blood at conversion.
We did not reveal any publications on tacrolimus effect on results of kidney transplantation in children in the accessible literature, which is why we considered reasonable to analyze our own clinical material and publish study data.

Statistical data manipulation

We program Statistica 6 and statistical package SPSS-10 for data manipulation. Statistical data manipulation involved such parameters as Kaplan-Meier cumulative survivability of recipients and transplants, Cox cumulative hazard level and log-rank test in order to perform comparative analysis. We appraised cumulative survivability of recipient and the transplanted kidneys, rates of transplant loss and mortality and relative cumulative risk of transplant loss or patient's death. We performed comparative analysis of transplant puncture biopsy sampling results in each of the groups 1 month after allotransplantation.

PATIENTS AND METHODS

This study is based on the observation of 58 children (group 1), who underwent 58 transplantations of kidneys from live relative donors from December 2000 to December 2012. Patients aged from 3 to 18 years (12.52±3.93 on the average). These patients were administered tacrolimus manufactured by Astellas (Japan) for immunosuppression; 19 patients were administered Advagraf, 39 – Prograf. The initial dose of the drug was 0.15 mg/kg per day; it was later corrected on the basis of concentration thereof in blood. Tacrolimus concentration was maintained at 2-8 ng/ml. Causes of chronic renal failure of the main group patients are given in tb. 1.

Control group included 58 patients aging from 1 to 18 years (10.81±4.94 on the average), who underwent 58 transplantations of kidneys from live relative donors within the same period. These patients were not administered tacrolimus for immunosuppression. Causes of chronic renal failure of the group 2 patients are given in tb. 2.

Induction immunosuppression in the main group patients involved such drugs as alemtuzumab (Campath) (51 patients; 87.93%), eculizumab (Soliris) (2 patients; 3.45%), daclizumab (Zenapax) (2 patients; 3.45%), in the group 2 patents – alemtuzumab (42 patients; 72.41%), eculizumab (13 patients; 22.42%), rituximab (Mabthera) (2 patients; 3.45%) and methylprednisolone (1 patient; 1.72%).

Although the amount of patients, who had been administered alemtuzumab for induction, is higher in group 1 than in group 2 (87.93 and 72.41%, respectively), statistical manipulation using Fisher's test demonstrated statistical insignificance of this difference ($\chi^2 = 3.47$; $p > 0.05$). As far as alemtuzumab was used in the overwhelming majority of patients in both groups, we may assume induction immunosuppression to be analogous in these patients. Scheduled therapy of the control group patients included cyclosporine A instead of tacrolimus, but remained the same apart from that (corticosteroids + mycophenolate mofetil).

STUDY RESULTS AND DISCUSSION

Calculation of the 5-year Kaplan-Meier cumulative survivability of the recipients (pic. 1) and the transplanted kidneys (pic. 2) demonstrated the following results: group 1 - 100±0.0 and 93.9±0.0%, group 2 – 77.8±0.93 and 72.2±1.08%, respectively. Statistical manipulation using log-rank test confirmed this statistical significance of this difference ($\chi^2 = 4.32$ and $p = 0.01581$; $\chi^2 = 4.71$ and $p = 0.02987$, respectively). Thus, survivability of the recipients and the transplanted kidneys is considerably higher in group 1 than in the control group.

Calculation of the cumulative allokidneys loss risk also demonstrated a far lower relative cumulative risk increment in group 1 than in group 2 (pic. 3). Cumulative fatal outcome risk follows the same trend (pic. 4).

Transplant loss and fatal outcomes

2 transplant losses (3.45%) were observed in group 1: 1 – due to rupture, 1 – due to acute rejection in the setting of chronic transplantation nephropathy. No fatal outcomes were observed in group 1.

6 transplant losses (10.43%) were observed in group 2: 3 (50%) – due to acute rejection, 2 (33.33%) – due to chronic transplantation and border-line alterations, 1 (16.67%) – due to the patient's non-compliance with the postoperative rehabilitation regimen. 11 fatal outcomes were observed in group 2: 4 – due to pneumonia, 3 – due to respiratory failure during artificial pulmonary ventilation, 1 – due to meningoencephalitis, 3 – due to cardiopulmonary arrest, 1 – due to cardiovascular failure, 1 – due to ascariasis. Cause of death of one patient is unknown.

Comparison of mortality rates (percentagewise) using Fisher's test demonstrated statistical significance of the difference - $\chi^2 = 1.21$, $p = 0.2717$ (pic. 5). The graph given in pic. 5 illustrates considerably lower rates of fatal outcomes and lost transplanted kidneys in group 1 than in group 2. We may, therefore, assert that Advagraf and Prograf positively affect results of living-related kidney transplantation.

Transplant puncture biopsy sampling results

The patients underwent transplant puncture biopsy sampling 1 month after the operation according to the protocol accepted in the international practice.
54 out of the 58 group 1 patients (93.1%) underwent this procedure. Morphological biopsy sample analysis results are given in tb. 3 and pic. 6.
49 out of the 58 control group patients (84.48%) underwent transplant puncture biopsy sampling. Comparison of biopsy sampling rates in groups 1 and 2 using Fisher's test demonstrated statistical insignificance of this difference ($\chi^2 = 1.39$, $p = 0.2391$); therefore, we may ignore this difference (tb. 4, pic. 7).
The given data indicate identical morphological nature of biopsy samples by almost all the parameters, as confirmed by χ^2 and *p* indices (tb. 5). Thus, we did not observe pronounced effect of tacrolimus on morphology of biopsy samples. It ought to be mentioned that the average rate of rejection per patient was almost the same in both groups: 0.42±0.53 in group 1 and 0.45±0.63 in group 2; $p = 0.7656$.
It is known that immunosuppressive therapy aimed at prevention or termination of rejections suppresses anti-infective immunity as well, as indicated by a high rate of infectious complications in the recipients of allotransplanted kidneys. That is why it is interesting to compare the rate of infectious complications in both groups: the rate varies from 0 to 23 (7.07±6.87 on the average) in group 1, from 0 to 42 (12.57±5.36 on the average) – in group 2. Statistical manipulation using Student's test demonstrated statistical significance of this difference ($p = 0.001024$); thus, tacrolimus is capable of providing sufficiently effective immunosuppression without pronounced suppression of the anti-infective immunity.

CONCLUSIONS

Thus, tacrolimus has become widely used for kidney transplantation both in adults and in children around the world. Most articles are dedicated to pharmacokinetics of the original drugs and analysis of the dose-concentration interconnection, especially when Prograf is substituted by Advagraf. Our study was aimed at determining, whether tacrolimus may be used for living-related kidney transplantation and if such is reasonable.
Results of comparative analyses demonstrated higher survivability rate and lower risk of transplant loss and patient's death in group 1 (patients, who had been receiving tacrolimus) than in the control group (patients, who had not been receiving the drug). Thus, tacrolimus is effective for immunosuppression after living-related kidney transplantation in children; its use is reasonable.

REFERENCES

1. Han D. J., Park J. B. et al. A 39-month follow-up study to evaluate the safety and efficacy in kidney transplant recipients treated with modified-release Tacrolimus (FK-506E)-based immunosuppression regimen. *Transplant Proc*. 2012; 44 (1): 115–117.
2. Kramer B. K., Charpantier B., Backman L. et al. Tacrolimus once daily (Advagraf) versus twice daily (Prograf) in de novo renal transplantation: a randomized phase III study. *Amer J Transplant.* 2010; 10 (12): 2632–2643.

3. Hougardy J. M., Broeders N., Klanda M. et al. Conversion from Prograf to Advagraf among kidney transplant recipients results in sustained decrease in tacrolimus exposure. *Transplantation*. 2011; 91 (5): 566–569.
4. Carcas-Sansuan A. J., Espinosa-Roman L., Almeda-Paulo G. N. et al. Conversion from Prograf to Advagraf in stable paediatric renal transplant patients and 1-year follow-up. *Pediatric Nephrology.* 2014; 29: 117–123.
5. Crespo M., Mir M., Marin M., Hurtado S. et al. De novo kidney transplant recipients need higher doses of Advagraf compared with Prograf to get therapeutic levels. *Transplant Proc.* 2009; 41 (6): 2115–2117.

Table 1. Causes of terminal stage of chronic renal failure in the group 1 patients

Primary disease diagnosis	Amount of patients (%)
Chronic glomerulonephritis	6 (11.34)
Vesicoureteral reflux + obstructive uropathy	16 (27.59)
Renal hypoplasia	5 (8.88)
Hemolytic-uremic syndrome	7 (12.07)
Nephrotic syndrome	7 (12.07)
Renal dysplasia	8 (13.79)
Focal segmental glomerulosclerosis	1 (1.97)
Polycystic kidney disease	2 (3.43)
Fanconi syndrome	1 (1.97)
Other diseases	4 (6.89)
Total	58 (100)

Table 2. Causes of terminal stage of chronic renal failure in the group 2 patients

Primary disease diagnosis	Amount of patients (%)
Chronic glomerulonephritis	7 (12.07)
Vesicoureteral reflux + obstructive uropathy	14 (24.14)
Renal hypoplasia	5 (8.63)
Hemolytic-uremic syndrome	6 (10.34)
Nephrotic syndrome	7 (12.07)
Renal dysplasia	6 (10.34)
Alport syndrome	1 (1.73)
Focal segmental glomerulosclerosis	2 (3.44)
Polycystic kidney disease	1 (1.73)
Fanconi syndrome	2 (3.44)
Other diseases	7 (12.07)
Total	58 (100)

Table 3. Results of morphological kidney biopsy sample analysis in the group 1 patients

Morphological diagnosis	Amount of cases (%)
Normal	29 (53.7)
Acute rejection	4 (7.42)
Border-line alterations	7 (12.96)
No rejection	14 (25.92)
Total	54 (100.0)

Table 4. Results of morphological kidney biopsy sample analysis in the group 1 patients

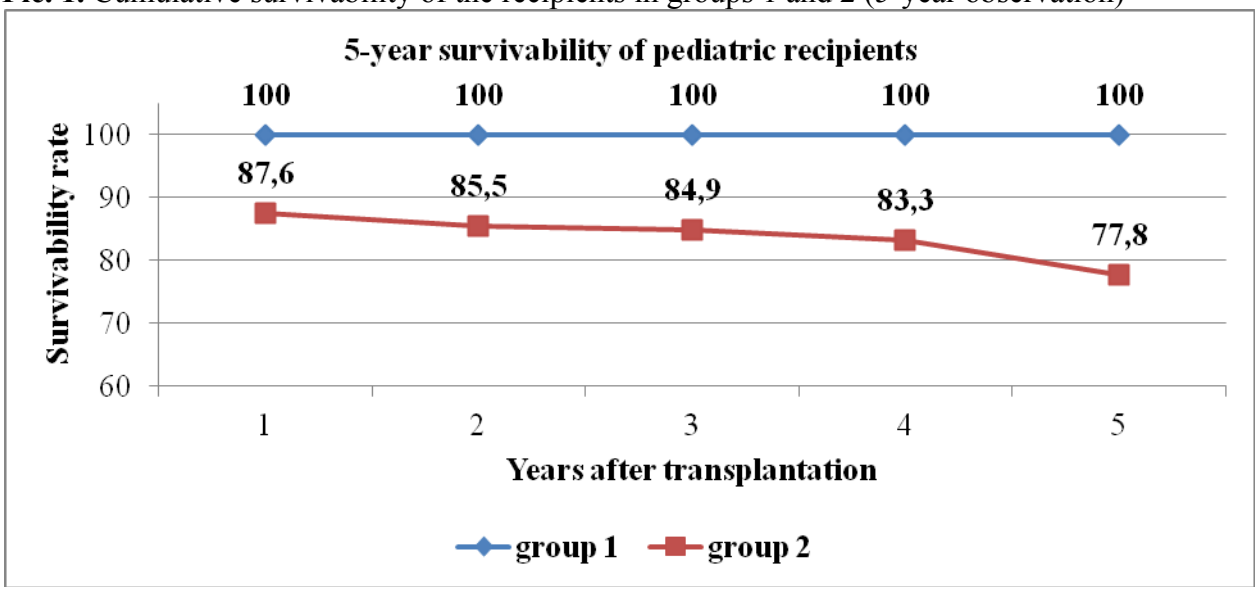
Morphological diagnosis	Amount of cases (%)
Normal	29 (53.7)
Acute rejection	4 (7.42)
Border-line alterations	7 (12.96)
No rejection	14 (25.92)
Total	54 (100.0)

Table 5. Morphological nature of biopsy samples in groups 1 and 2

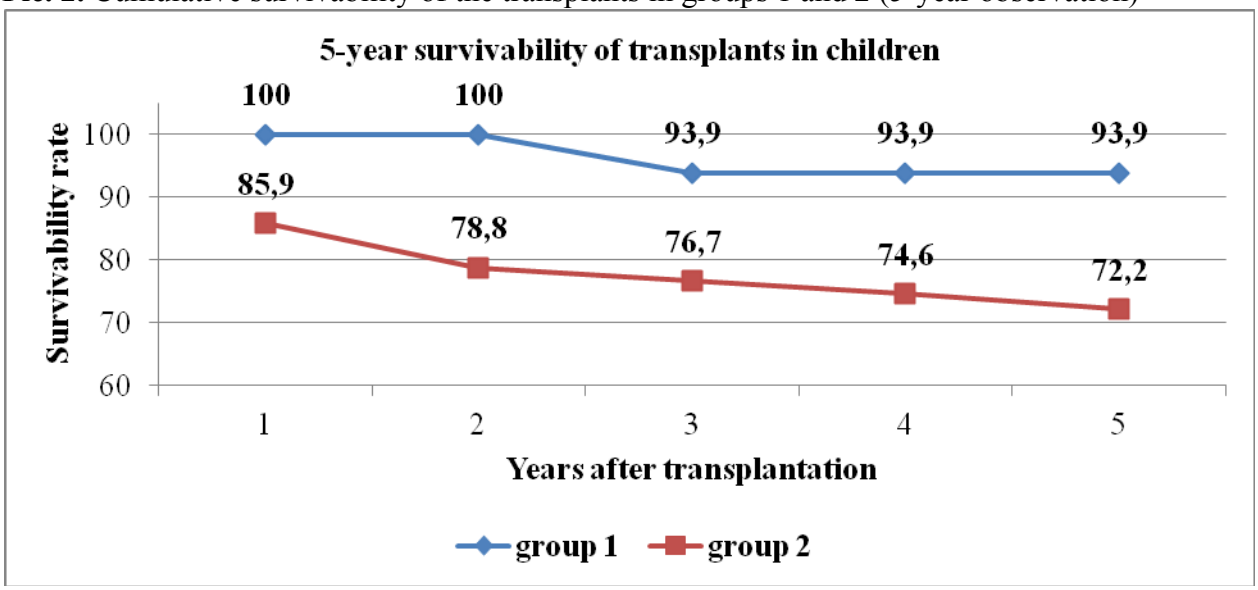
Morphological diagnosis	Group 1, %	χ^2	p	Group 2, %
Normal	53.7	0.24	0.6252	46.93

Cyclosporine toxicity	0	-	-	4.08
Acute rejection	7.41	1.89	0.1669	18.37
Border-line alterations	12.96	0.04	0.8386	16.33
No rejection	25.92	1.49	0.2226	14.29
Total	100.0			100.0

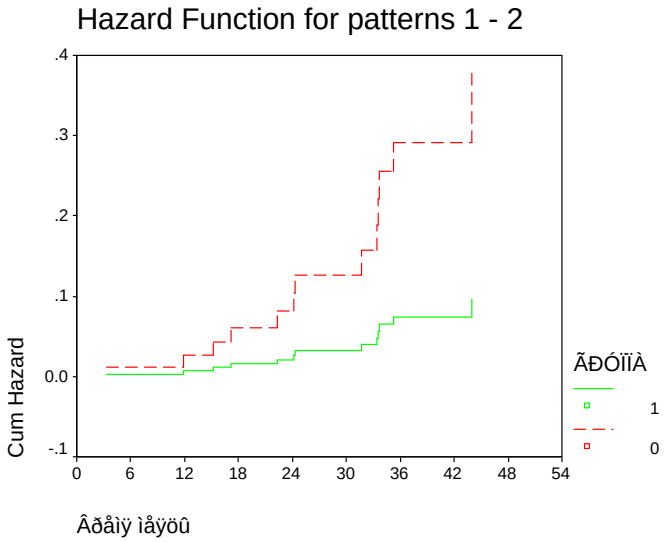
Pic. 1. Cumulative survivability of the recipients in groups 1 and 2 (5-year observation)



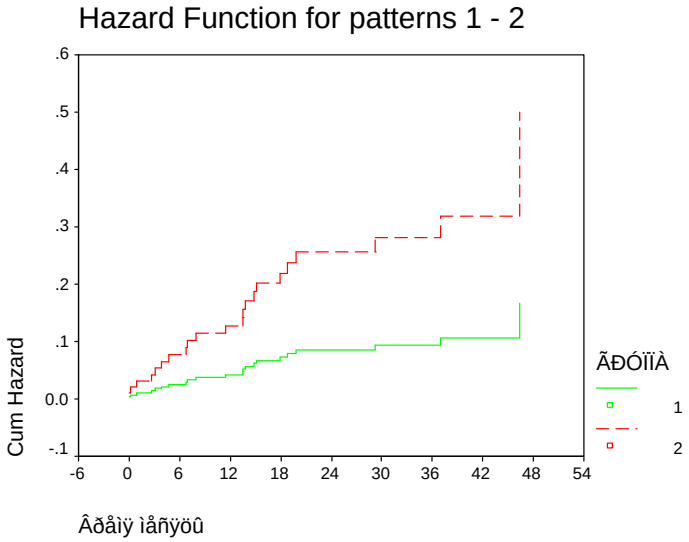
Pic. 2. Cumulative survivability of the transplants in groups 1 and 2 (5-year observation)



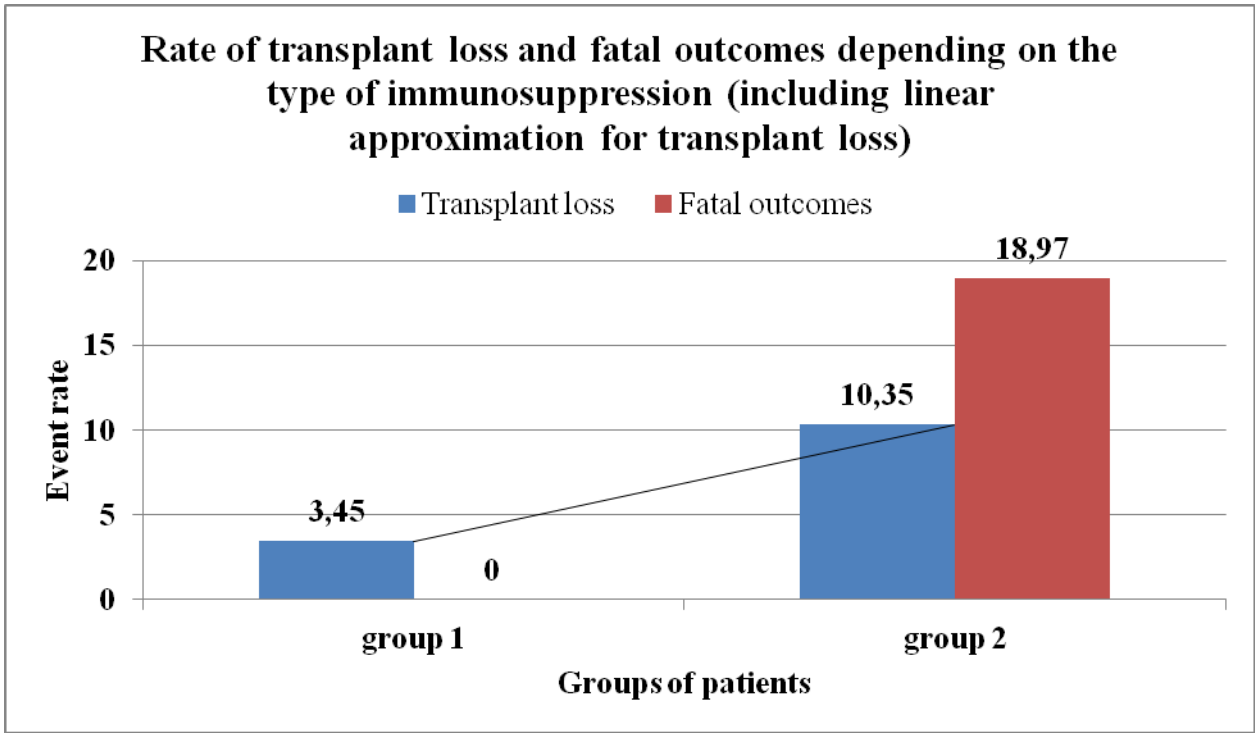
Pic. 3. Cumulative transplant loss risk function for groups 1 and 2. EVENT – KIDNEY LOSS



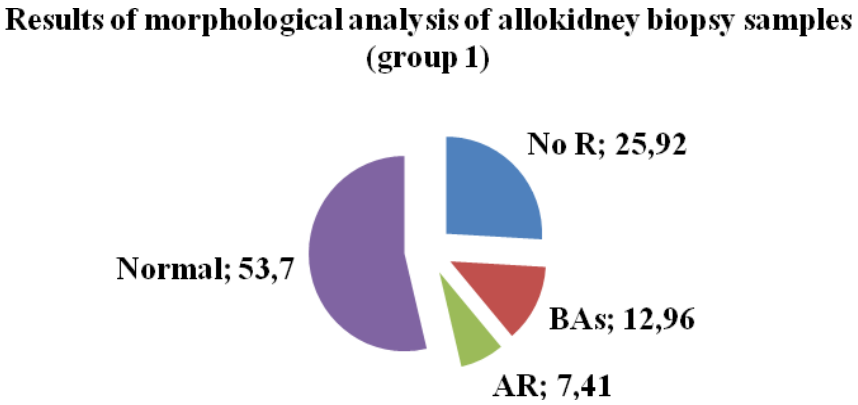
Pic. 4. Cumulative fatal outcome risk function for groups 1 and 2. EVENT – DEATH



Pic. 5. Comparative analysis of the rate of fatal outcomes and allokidneys loss depending on the type of immunosuppression

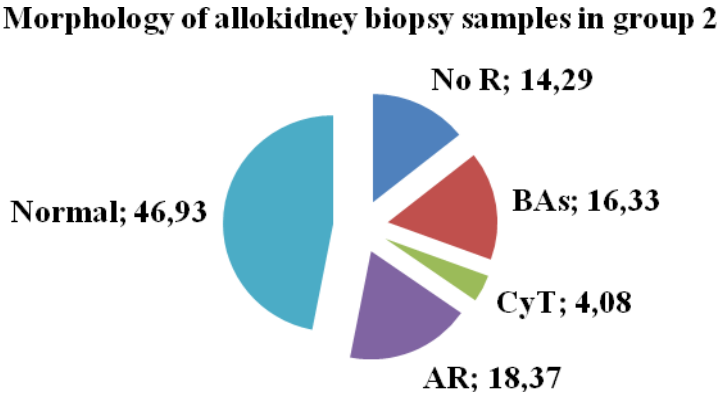


Pic. 6. Morphological analysis of allokidney biopsy samples in group 1



Note. No R – no rejection, BAs – border-line alterations, AR – acute rejection.

Pic. 7. Morphological analysis of kidney biopsy samples in group 2



Note. No R – no rejection, BAs – border-line alterations, AR – acute rejection.