Transpl Int (1997) 10: 13–18

ORIGINAL ARTICLE

Marie Felldin
Lars Bäckman
Christina Brattström
Öystein Bentdal
Knut Nordal
Kerstin Claesson
Nils H. Persson

Rescue therapy with tacrolimus (FK 506) in renal transplant recipients – a Scandinavian multicenter analysis

Received: 13 November 1995
Received after revision: 8 July 1996
Accepted: 13 September 1996

M. Felldin
Division of Nephrology,
Sahlgrenska University Hospital,
S-41345 Göteborg, Sweden

L. Bäckman (✉)
Division of Transplantation,
and Liver Surgery,
Sahlgrenska University Hospital,
S-41345 Göteborg, Sweden
Fax: + 46 31 820 557

C. Brattström
Department of Transplantation Surgery,
Karolinska Institute, Huddinge Hospital,
S-14186 Huddinge, Sweden

Ö. Bentdal
Department of Transplantation Surgery,
Rikshospitalet, Pilestredet 32,
N-0027 Oslo, Norway

K. Nordal
Department of Internal Medicine,
Rikshospitalet, Pilestredet 32,
N-0027 Oslo, Norway

K. Claesson
Department of Transplantation Surgery,
Uppsala University Hospital,
S-75185 Uppsala, Sweden.

N. H. Persson
Department of Vascular and Renal
Diseases,
Malmö University Hospital,
S-20502 Malmö, Sweden

Abstract All renal allograft recipients ($n = 32$) in Sweden and Norway who were converted from cyclosporin(CyA)-based immunosuppression to FK 506 (tacrolimus) between October 1992 and June 1995 were analyzed retrospectively. The reasons for conversion were acute refractory rejection ($n = 21$), chronic rejection ($n = 4$), and suspected CyA toxicity ($n = 6$); one patient was converted for psychological reasons. The mean time from transplantation to conversion was 29 (range 1–243) weeks and there was a mean follow-up of 46 (2–143) weeks. Overall graft survival was 59 %, with graft survival 52 % in patients converted because of acute rejection, 50 % in patients converted because of chronic rejection, and 83 % in patients converted because of CyA toxicity. There was no significant correlation between preconversion serum creatinine and outcome. Seventy-two percent of the patients had significant side effects during FK 506 treatment, the most frequent ones being neurological and gastrointestinal symptoms. These improved after dose reduction. Two patients became overimmunosuppressed and developed lymphoma. One patient died of the primary kidney disease, hemolytic uraemic syndrome. We conclude that FK 506 therapy is able to salvage kidneys with acute refractory rejection and that it is an alternative in patients with CyA toxicity. However, the risk of overimmunosuppression must be considered.

Key words Kidney transplantation, conversion, Tacrolimus · Cyclosporin, acute rejection, chronic rejection

Introduction

Despite the use of cyclosporin A (CyA)-based immunosuppression protocols, the graft rejection rate after kidney transplantation is around 50 % [1]. FK 506 is a macrolide lactone produced by the fungus *Streptomyces tsukubaensis* with immunosuppressive activity. FK 506 has a completely different molecular structure than CyA, but both drugs inhibit the same step in T-cell activation. FK 506 produces somewhat different side effects than CyA – mainly neurological and gastrointestinal problems – but both drugs are nephrotoxic [7]. FK 506 has proven to be more effective than CyA-based immunosuppression both as "rescue therapy" in patients with steroid-resistant rejection and as primary immunosuppression, with few-

er rejection episodes in liver allograft recipients [3, 10].

A prospective comparison between FK 506 and CyA as primary immunosuppression in kidney transplantation is currently in progress, but the results have not yet been published. A nonrandomized study comparing patients treated with CyA or FK 506 as primary immunosuppression after kidney transplantation found no difference in graft survival, graft function, or rejection rate between the two groups [8]. The same group also published data on FK 506 as "rescue therapy" in renal allograft recipients with steroid-resistant rejection [6]. Fifty-seven of the 77 patients' grafts (74%) were salvaged after conversion to FK 506 after a mean follow-up of 14 months.

The aim of this study was to analyze the outcome of FK 506 as rescue therapy in CyA-treated kidney transplant recipients with refractory acute rejection, chronic rejection, or severe CyA toxicity.

Patients and methods

Thirty-two renal allograft recipients (11 women and 21 men) with a mean age of 38 (range 1.5–65) years were converted to tacrolimus (FK 506) from CyA-based immunosuppression in Sweden and Norway between October 1992 and June 1995. Data was obtained retrospectively. The reasons for conversion were acute refractory rejection ($n = 21$), chronic rejection ($n = 4$), and suspected CyA-related adverse events ($n = 6$). One patient had been treated with FK 506 during a previous transplantation as part of a clinical trial and wanted the same therapy. The mean follow-up was 46 (range 2–143) weeks. Graft loss was diagnosed at the time dialysis was started or at the time of transplantectomy or retransplantation. Patients' demographics and underlying kidney diseases are shown in Tables 1 and 2.

Primary immunosuppression consisted of CyA, prednisolone, and azathioprine (AZA; $n = 16$). Eleven patients received a quadruple sequential regimen [CyA, prednisolone, AZA, and polyclonal antilymphocyte/antithymocyte (ALG) preparations]. Three patients were treated with CyA, steroids, and ALG, and two patients with CyA and prednisolone alone. All rejection episodes were diagnosed by biopsy and classified accoring to the Banff criteria [9]. Biopsy findings in the acute rejection group were acute vascular rejection (lymphocytic infiltration in arterial walls and/or intraglomerular hemorrhage, $n = 9$), Banff I ($n = 4$), and Banff II ($n = 8$). New onset of hyaline arteriolar thickening and/or vacuolization of tubules in biopsy was considered indicative of CyA toxicity. Chronic rejection was characterized as interstitial fibrosis and tubular atrophy.

The mean time from transplantation to conversion to FK 506 was 29 (range 1–243) weeks. Patients with acute rejection were converted 13 (range 3–94) weeks after transplantation and, of these, 66% (14/21 patients) within the first 8 weeks postoperatively. Patients with chronic rejection were converted at 21, 25, 69, and 243 weeks, respectively, after transplantation. The six patients with CyA toxicity were converted after a mean of 52 (range 1–178) weeks.

All patients in the acute rejection group had received high-dose steroids as antirejection therapy either alone ($n = 6$, 28%) or in combination with ALG and/or OKT3 ($n = 12$, 58%) or with plasmapheresis ($n = 3$, 15%). The median number of antirejection treatments was 2 (range 1–4) before conversion to FK 506. The patients with chronic rejection were given high-dose corticosteroids ($n = 2$) and steroids with ALG ($n = 1$), while one patient did not receive any antirejection therapy at all before conversion to FK 506.

Table 1 Demographics in patients converted to FK 506 because of acute rejection, chronic rejection, or CyA toxicity

	Acute	Chronic	CyA toxicity
Primary transplant recipients ($n = 19$)	12	4	3
Second transplant recipients ($n = 11$)	8	0	3
Third or fourth transplant recipients ($n = 2$)	2	0	0
Kidney and pancreas recipients ($n = 3$)	3	0	0
Living related donor ($n = 5$)	2	2	1

Table 2 Underlying kidney diseases in all patients converted to FK 506

	n
Chronic glomerulonephritis	11
Diabetes mellitus	5
Adult polycystic kidney disease	3
Chronic pyelonephritis	3
Vasculitis/lupus nephritis	2/2
Nephronophthisis	2
Congenital malformation	2
Hemolytic uremic syndrome	1
Unknown	1

Adverse events associated with CyA included nephrotoxicity and were revealed by biopsy in two patients. One of these patients suffered four rejection episodes prior to conversion, and these were treated with SoluMedrone, OKT3, and plasmapheresis. Other suspected CyA-associated events were thrombotic thrombocytopenic purpura ($n = 1$), severe hirsutism ($n = 1$), and severe gingival hyperplasia ($n = 1$). Two of these patients had mild acute rejection at the time of conversion although their serum creatinine (s-crea) was within the normal range. They received one course of high-dose steroids each. The sixth patient in this group was a 21-month-old girl who underwent kidney transplantation due to hemolytic uremic syndrome (HUS). Shortly after transplantation HUS recurred, and when it was thought that the hemolysis might be worsened due to CyA, the patient was converted to FK 506.

At the time of conversion, the mean s-crea was 334 (range 76–742) μmol/l normal s-crea is 55–115 μmol/l). Three patients were on dialysis. In patients with acute rejection, the mean s-crea was 369 (range 115–671) μmol/l, and in the four patients with chronic rejection it was 316 (249–389) μmol/l. In patients with CyA-associated adverse effects, the mean s-crea was 174 (76–361) μmol/l, excluding the patient who was dialysis-dependent and including three patients with normal s-crea at the time of FK 506 conversion.

FK 506 was given p.o. every 12 h in a mean dose of 0.27 ± 0.06 mg/kg body weight per day. The dose was then adjusted according to efficacy and signs of toxicity. Whole blood levels were analyzed using the IMx-method [4]. CyA and AZA treatment was discontinued the same day FK 506 treatment was started.

The Wilcoxon signed-rank test was used for the statistical analysis. Values are expressed as mean ± SD or, when listed, mean (range).

Results

Patient survival

A 21-month-old girl who was converted to FK 506 because of recurrence of HUS in the transplant died during FK 506 treatment. The syndrome was too far advanced and the child died because of her underlying kidney disease 7 weeks after conversion. The FK 506 treatment was not considered to have been related to her death. The remaining 31 patients (97 %) are alive.

Graft survival

The overall graft survival was 59 % after a mean follow-up of 46 (range 2–143) weeks. In patients converted because of acute rejection, the graft survival rate was 11/21 (52 %). In patients converted because of chronic rejection 2/4 (50 %), and in the CyA toxicity group, the graft survival rate was 5/6 (83 %). The major cause of graft loss was rejection (n = 10). Two grafts were lost because the patients developed lymphomas, and the last graft was lost due to recurrent HUS. Graft loss in the total group occurred at a mean of 18 (range 1–80) weeks after the conversion. In the acute rejection group, the graft loss occurred 14 (range 1–80) weeks after the conversion, while the two patients with chronic rejection lost their grafts 19 and 49 weeks, respectively, after the conversion.

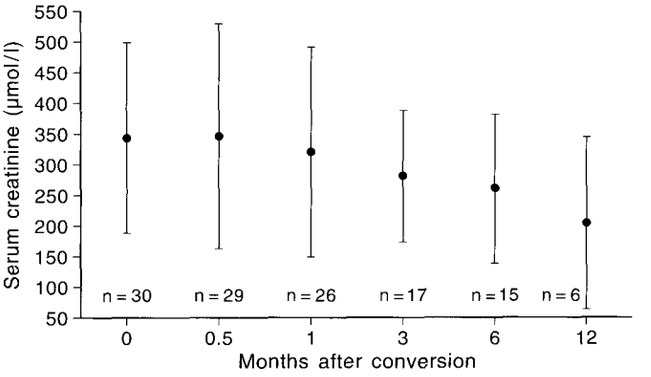

Fig. 1 Mean s-crea level (± 1SD) after conversion to FK 506 of total group except for two patients already dialysis-dependent at conversion

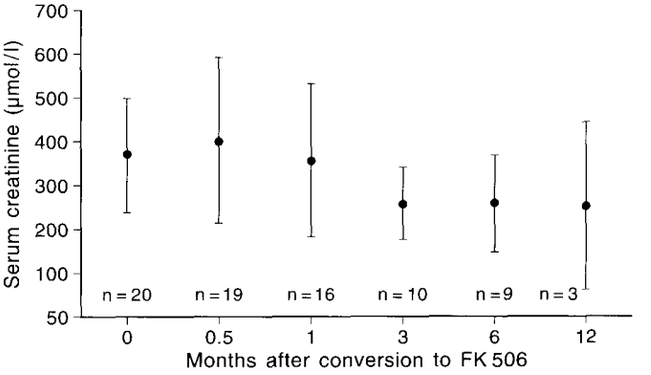

Fig. 2 Mean s-crea level (± 1SD) after conversion in the acute rejection group

Renal function and follow-up

Among the 19 patients with functioning grafts, the mean s-crea level was 220 (range 104–351) µmol/l at the end of the study period. The development of s-crea in the total group and in the acute rejection group is shown in Figs. 1 and 2. In patients converted because of acute rejection, the mean s-crea was 232 (range 104–351) µmol/l after a mean follow-up of 43 (range 2–89) weeks. Two patients in this group were dialysis-dependent at the time of conversion. One of them had a functioning graft with a s-crea level of 250 µmol/l 17 weeks after conversion. The two patients with chronic rejection and functioning grafts had s-crea levels of 223 and 240 µmol/l, 7 and 60 weeks, respectively, after conversion. In the CyA toxicity group, mean s-crea was 233 (range 114–259) µmol/l after 2, 6, 60, 73 weeks and almost 3 years (143 weeks) of follow-up after conversion.

The two patients with hirsutism and gingival hyperplasia improved after the conversion. The patient with thrombocytopenic purpura still has ongoing hemolysis and declining graft function. None of these patients have developed signs of rejection since conversion. CyA nephrotoxicity (diagnosed by core needle biopsy) that was seen in two patients has been reversed. The first patient now has a normal s-crea and the second patient improved shortly after conversion. They were, however, not re-biopsied after conversion. The patient who had been treated with FK 506 during a previous transplantation as part of a clinical trial was converted 10 days post-transplantation at a s-crea level of 740 µmol/l due to acute tubular necrosis. At 1 year the s-crea is 315 µmol/l.

There was no correlation in the total material or in the three subgroups between s-crea level before or 1 month after conversion and outcome. Outcome is summarized in Table 3.

FK 506 dosing and whole blood levels

The initial mean FK 506 dose was 0.27 mg/kg body weight per day. Figure 3 illustrates the continuous decrease in FK 506 level after conversion from a mean

Table 3 Results after conversion ot FK 506 in the whole group and in patients converted because of acute rejection, chronic rejection, or CyA toxicity[a]

	Total ($n = 32$)	Acute ($n = 21$)	Chronic ($n = 4$)	CyA ($n = 6$)
Follow-up, mean (range) in weeks	46 (2–143)	43 (2–89)	33 (7–60)	57 (2–143)
Patient survival, n (%)	31 (97 %)	21 (100 %)	4 (100 %)	5 (83 %)
Graft survival, n (%)	19 (59 %)	11 (52 %)	2 (50 %)	5 (83 %)
S-crea level at switch (μmol/l)	343 (76–742)	369 (115–671)	316 (249–389)	174 (76–361)
S-crea level at follow-up (μmol/l)	220 (104–351)	232 (104–351)	233 (226, 240)[b]	172 (114–259)

[a] One patient converted for another reason was excluded from the subgroups
[b] Two patients, respectively

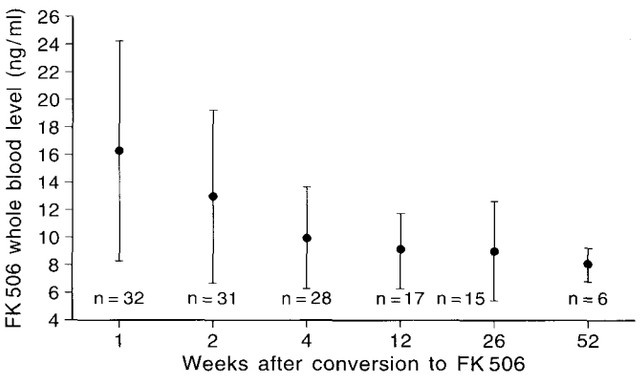

Fig. 3 Mean FK 506 whole blood level (mean ± 1SD; IMx Analyzer) after conversion. There was a significant ($P = 0.002$) reduction after 1 month

level of 16 ng/ml after 1 week. No correlation was found between initial FK dose, FK 506 whole blood level, and outcome.

At the time of graft failure, the FK 506 treatment was discontinued, and those patients who were considered to be in need of continued immunosuppression were converted back to CyA.

Side effects

Twenty-three patients (72 %) were reported to have side effects and complications during FK 506 treatment. Most common were different signs of central nervous system toxicity. There were also different gastrointestinal symptoms (Table 4). These were reversed by dose reduction, although the patients with peptic ulcers needed medication. Nephrotoxicity was reported in three patients, one biopsy-verified (interstitial fibrosis), the others diagnosed clinically (i.e., an increase in s-crea). None of these three patients had previously had CyA-associated nephrotoxicity. The FK 506 whole blood levels at the time were 46, 40, and 23 ng/ml.

Two patients developed lymphomas. One patient converted to FK 506 5 weeks post-transplantation was treated with high-dose steroids, ALG, and OKT3 because of acute rejection before conversion. One week later, a transplantectomy was performed. The histopathological examination showed a B-cell lymphoma. During the postoperative period, the patient also developed a positive IgM Epstein-Barr virus titer. The second patient had a vascular rejection and a suspected thrombocytopenic purpura, presumably due to CyA 4 weeks post-transplantation. He was then treated with plasmapheresis, OKT3, cyclophosphamide, and steroids before conversion. Seven months later he presented with fever, abdominal pain, and graft failure. Further investigation showed a non-Hodgkin T-cell lymphoma in the small bowel. The patient underwent transplantectomy and small bowel resection and is alive without evidence of malignant disease after a follow-up of 18 months.

One 49-year-old male patient experienced worsening ischemic heart disease during the FK 506 treatment. Another 53-year-old male patient developed both coronary infarction and compartment syndrome in the right calf after 7 months of FK 506 treatment. Except in the case of the two lymphomas, none of these side effects led to the discontinuation of FK 506 and all but the two were managed by a reduction in the FK 506 dose.

Discussion

Tacrolimus is a relatively new immunosuppressive agent with promising results after liver and kidney transplantation. In an open study from Pittsburgh, 74 % of 77 renal allografts with acute refractory rejection were still functioning with a mean s-crea of 210 μmol/l after a mean follow-up of 14 months after conversion to FK 506. Nine of the 18 patients were on dialysis at the time of conversion [6].

Our patient survival was good: 97 %. The overall graft survival was 59 %. In patients with acute refractory rejection, graft survival was 52 %, which is not as good as the results reported from Pittsburgh [6]. Our patients with acute rejection were followed for a comparable time

Table 4 Reported side effects and complications during FK 506 treatment

Type	*n*	
CNS toxicity	13	
Headache		5
Tremor		5
Vertigo		1
Ataxia and seizure		1
Serous meningitis		1[a]
Gastrointestinal symptoms	9	
Diarrhea		5
Gastritis		2
Peptic ulcer		1
Diverticulitis		1
Infections	7	
Pneumonia		1
Septicemia		2
CMV infection	2	
Urinary tract infection		2
Nephrotoxicity	3	
Lymphoma	2[a]	
Diabetes mellitus	2	
Ischemic heart disease	2	
Compartment syndrome	1	
Sweating of the palms	1	
Orthostatism	1	

[a] These patients were treated with OKT3 before conversion to FK 506

(11 months) and had a comparable s-crea level at follow-up (232 μmol/l). However, the mean s-crea in our patients was 370 μmol/l at conversion compared to 280 μmol/l in the Pittsburgh study, and acute vascular rejection was seen in 43 % of our patients compared to 26 % in Pittsburgh. This could indicate that we converted our patients later in the course. Fewer of our patients received ALG (79 % vs 58 %), which might also have influenced the results. However, two of our patients developed lymphoma as a sign of overimmunosuppression.

Chronic rejection as a cause of conversion was seen in only four patients, although one patient was treated with FK 506 1 year before graft failure. One of the two still functioning grafts has been followed for over 1 year with stable graft function.

Six patients were converted to FK 506 because of adverse effects of CyA. Graft function is good in this subgroup. The conversion was beneficial for patients with severe nephrotoxicity, hirsutism, and gingival hyperplasia. FK 506, therefore, seems to be an alternative in patients with advanced or intolerable side effects of CyA. The patient with thrombocytopenic purpura was not cured by the conversion to FK 506, suggesting either that CyA was not the cause or that the two drugs have similar mechanisms and capacity for inducing this disease.

The major cause of graft loss was rejection. Two patients (6 %) developed lymphomas; they apparently paid the price of overimmunosuppression given prior to the conversion.

Like Jordan et al. [6], we were not able to find any correlation between s-crea levels at time of conversion or after 1 month and graft survival. Nor was there any correlation between the initial FK 506 dose or whole blood level and outcome.

We did find a high incidence of neurological complications in patients converted to FK 506, predominantly tremor and headache (Table 4). Two patients had vertigo and ataxia with seizure. All of these symptoms were improved by dose reduction. One patient presented with serous menigitis, but this was most probably caused by OKT3 that was administered at the same time. Gastrointestinal symptoms were also common, in particular, diarrhea, which was a self-limiting symptom. Significant infections (pneumonia, urinary tract infections, septicemia, and CMV infections including retinitis) were reported in seven patients. Three patients developed insulin-dependent diabetes mellitus shortly after the conversion to FK 506. Another patient had to be treated with insulin for 5 days 8 weeks after conversion; after that his blood glucose normalized. Seven patients (23 %) were in need of stronger antihypertensive treatment after conversion. Both blood glucose level and hypertension are difficult to interpret in these types of patients since they also receive high doses of steroids and have reduced kidney function which, in itself, can cause these signs and symptoms. The total number of side effects and complications was high among our FK 506-treated patients, and this has also been described earlier [3, 10]. In liver transplant recipients it has been shown that nephrotoxicity as well as severe neurotoxicity correlate with FK 506 levels in plasma [2]. The Japanese FK 506 Study Group found a positive correlation between high FK 506 whole blood trough concentration and adverse effects, as well as a correlation between low FK 506 concentration and rejection [5]. In our analysis, it was not possible to correlate FK 506 whole blood level and side effects since these data are not complete.

In our experience, FK 506 was not as successful as rescue therapy in renal transplant recipients as reported in liver transplant recipients. One explanation for this difference could be the ability of the liver to regenerate after being damaged and, consequently, to better manage the trauma of severe rejection once the inflammatory response has been overcome. Since the kidney lacks this capability, it is more vulnerable to the same kind of trauma. Jordan et al. reported a higher success rate in rescue treatment with FK 506 in renal allograft recipients than we did; however, this could be explained by differences in patient population and severity of rejections at the time of transplantation.

In summary, we found that FK 506 could be considered in cases of acute refractory rejection. The success

rate may increase if FK 506 is introduced earlier in the course of acute rejection. FK 506 is also an alternative in cases of CyA toxicity. The drug seems to be less successful in cases of chronic rejection.

Acknowledgement The authors express their gratitude to the Swedish Society for Patients with Kidney Diseases for. This study was supported by a grant from the Swedish Society for patients with kidney diseases.

References

1. Almond PS, Gillingham KJ, Sibley R, Moss A, Melin M, Leventhal J, Manivel C, Kyriakides P, Payne WD, Dunn DL, Sutherland DER, Gores PF, Najarian JS, Matas AJ (1992) Renal transplant function after 10 years of cyclosporine. Transplantation 53: 316–323
2. Bäckman L, Nicar M, Levy M, Distant D, Eisenstein C, Renard T, Goldstein R, Husberg B, Gonwa TA, Klintmalm G (1994) FK506 trough levels in whole blood and plasma in liver transplant recipients. Transplantation 57: 519–525
3. European FK506 Multicenter Liver Study Group (1994) Randomised trial comparing tacrolimus (FK506) and cyclosporine in prevention of liver allograft rejection. Lancet 344: 423–428
4. Grenier FC, Luczkiw J, Bergmann M, Lunetta S, Morrison M, Blonski D, Shoemaker K, Kobayashi M (1991) A whole blood FK 506 assay for the IMx® analyzer. Transplant Proc 25: 2748–2749
5. Japanese FK 506 Study Group (1993) Japanese study of FK506 on kidney transplantation: results of late phase II study. Transplant Proc 25: 649–654
6. Jordan M, Shapiro R, Vivas CA, Scantlebury VP, Rhanhawa P, Carrieri G, McCauley J, Demetris AJ, Tzakis A, Fung JJ, Simmons RL, Hakala TR, Starzl TE (1994) FK 506 "rescue" for resistant rejection of renal allografts under primary cyclosporine immunosuppression. Transplantation 57: 860–865
7. Lu CY, Sicher SC, Vazquez MA (1993) Prevention and treatment of renal allograft rejection: new therapeutic approaches and new insights into established therapies. J Am Soc Nephrol 4: 1239–1256
8. Shapiro R, Jordan M, Scantlebury V, Fung J, Jensen C, Tzakis A, McCauley J, Carroll P, Riccordi C, Demetris AJ, Mitchell S, Jain A, Iwaki Y, Kobayashi M, Reyes J, Todo S, Hakala TR, Simmons RL, Starzl TE (1991) FK 506 in clinical kidney transplantation. Transplant Proc 23: 3065–3067
9. Solez K, Axelsen RA, Benediktsson H, Burdick JF, Cohen AH, Colvin RB, Croker BP, Droz D, Dunhill MS, Halloran PF, Häyry P, Jennette JC, Keown PA, Marcussen N, Mihatsch MJ, Morozumi K, Myers BD, Nast CC, Olsen S, Racusen LC, Ramos LE, Rosen S, Sachs DH, Salomon DR, Sanfilippo F, Verani R, Willebrand E von, Yamaguchi Y (1993) International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. Kidney Int 44: 411–422
10. US Multicenter FK 506 Liver Study Group (1994) A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med 331: 1110–1115