Content

INTRODUCTION

Kidney transplantation is the best method of therapy for patients with end-stage renal disease. Important advances in immunosuppressive therapy, HLA typing and surgical techniques have resulted in a better one-year survival of transplanted organs. However, the fate of renal allografts has not been substantially changed in the long-term [1]. Despite the rising successes in organ transplantations, both acute and chronic rejections remain the main complications after kidney transplantation.

Acute rejection may occur anytime after kidney transplantation, but it mainly occurs during first three months. Clinical features are graft function deterioration, graft enlargement and the failure of blood circulation within the graft. The diagnosis is based on histological examination of the allograft tissue. Acute rejection occurs in 20-30 % of kidney graft recipients during the first weeks after transplantation and it is important risk factor for the development of chronic allograft nephropathy (CAN). CAN, reclassified as interstitial fibrosis and tubular atrophy (IF/TA), is the most common cause of kidney graft failure [2-4]. Molecular and immunological mechanisms of CAN development are not quite clearly understood.

The pathogenesis of rejection is a complex process with a broad spectrum of cytokines and chemokines involved. Candidate genes and their role in rejection episodes as well as in the failure of transplanted

organ have been studied. These include transforming growth factor-beta (TGF-β), tumour necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interlukins 6 and 10 (IL-6, IL-10) and chemokines RANTES (regulated upon activation normal T-cell expressed and secreted), monocyte chemotactic protein-1 (MCP-1), their receptors CCR2 and CCR5 and others. The expression levels of these molecules vary during the post transplant time and also due to various pathological situations in the kidney allograft. Recently, numerous polymorphisms in growth factors, cytokines, chemokines and their receptors genes have been identified. Polymorphisms in the promotor region of gene influence its transcription and the protein production level.

In recent years, some genes involved in the up-regulation in acute rejection and in CAN have been identified. In acute rejection, the up-regulation of effector molecules of cytotoxic T-lymphocytes perforin, granzyme B and Fas ligand have been identified and TGF-β was shown to play important role in CAN [5,6]. However, the role of cytokines and chemokines in rejection episodes is not quite clear yet. Previous literature had shown the enhanced expression of IL-2 and IL-10 in kidney allograft during acute rejection [6-8]. Other studies, however, did not confirm these results [9]. In addition to TGF-β, there was also shown an increased expression of TNF-α, IL-7 and IL-15 in CAN [9-12]. It is necessary to note that the results of numerous studies are not

congruent. From the broad spectrum of chemokines, the role of RANTES, MCP-1, MIP-1α (macrophage inflammatory protein) and MIP-1β in rejection episodes [13-15] has been confirmed. RANTES is expressed at the early stages after transplantation and MCP-1 especially at late stages after kidney transplantation [16,17].

Provided that the role of polymorphisms of some candidate genes in the graft nephropathies and the risk of rejection is confirmed, kidney graft recipients predisposed to the risk of rejections could be identified as early as on the waiting list stage and thus would potentially benefit from tailored immunosuppression. However, the existing studies showed questionable and in some cases also had dissimilar results.

One aim of this submitted dissertation was to find the influence of polymorphisms in selected genes (TNF-α-308G/A, MCP-1-2518A/G, RANTES-403G/A, -109T/C, -28C/G, CCR2+190G/A, IFN-γ+874A/T, TGF-β1-869T/C, +915G/C a CCR5Δ32) on kidney graft outcome by studying a large cohort of well-characterized patients who underwent renal transplantation. Other aim was to find if the analysis of intrarenal mRNA expression of selected genes (TGF-β1, TNF-α, IL-6, IL-10, MCP-1 a RANTES) could help in the diagnostics based on the histological examination of allograft tissue, and if it would be possible to guess the prognosis of disease according to their intrarenal expression.

PATIENTS AND METHODS

Patients

157 kidney transplantations were performed in year 1999, 169 in 2000, 174 in 2001, 167 in 2002, 183 in 2003 and 216 in 2004 at the Transplant Centre of the Institute for Clinical and Experimental Medicine. Most kidney graft recipients undergo one or more kidney allograft biopsy carried out for diagnostical purposes or according protocol l2 months (presently 3 months) after kidney transplantation. For the purpose of this study, we used 174 biopsies where the sufficient material for RNA isolation was available, from 430 biopsies performed between November 2001 and June 2003. Cyclosporine A was the cornerstone immunosuppressant in 60 % of them (in combination with corticosteroids and mycophenolate mofetil or azathioprine), 30 % of patients were treated by tacrolimus (in combination with corticosteroids and mycophenolate mofetil or azathioprine) and the others were treated by sirolimus or azathioprine.

All patients gave their written informed consent to participate in the study, were regularly followed and their renal function was monitored up to 42 months after the renal biopsy.

436 patients were also included into the study, which underwent kidney transplantation at IKEM between 1999 and 2004 and gave their consent to use their DNA for analysis of gene polymorphisms.

Additionally, 173 patients out of this cohort underwent a protocol biopsy 12 months after kidney transplantation.

Clinical data

The following clinical variables were recorded from the patients: gender, age at the time of transplantation, donor age, the origin of kidney graft (deceased- or living-donor), the number of HLA mismatches, maximal panel-reactive antibodies, serum creatinine, GFR estimated using the Cockcroft-Gault formula [18], proteinuria, serum cholesterol and triglycerides levels, the occurrence of diabetes mellitus and hypertension, use of angiotensin-converting enzyme (ACE) inhibitors, use of hypolipidemics, the history of acute rejection and delayed graft function incidence (defined as a need of post-transplant dialysis).

Renal biopsies and histomorphology

All biopsies were done by a 14G tru-cut needle (Uni-Cut Nadeln, Angiomed, Germany) guided by ultrasound (Toshiba, Power Vision 6000, Japan). Small portions of renal tissue from the cortex or juxtamedulary zone were immediately frozen in liquid nitrogen and stored at -80°C for expression analysis, while most of the renal tissue taken by core biopsy was used for routine histology performed by the standard method. Tissues were fixed in 10% formalin for 15-30 min

and then processed in TPC 15 tissue processor (MEDITE Histotechnik, Germany). Four μm thick paraffin embedded tissue sections were stained with hematoxylin and eosin, periodic acid-Schiff (PAS), aldehyde-fuchsin orange G (AFOG), Sirius red with elastic stain and periodic acid silver-methenamine (PASM). Biopsy tissues were scored on the basis of the Banff 97 working classification [19]. Biopsies were divided into the groups according to histological finding: normal finding (control group), borderline changes, acute rejection, CAN, acute tubular necrosis (ATN), recurrence of glomerulonephritis and toxicity of calcineurin inhibitors.

RNA isolation and real-time quantitative RT-PCR

The renal tissue was homogenized, total RNA was extracted using a StrataPrep® Total RNA Microprep Kit (Stratagene, La Jolla, USA) and reverse transcribed into complementary DNA (cDNA), using SuperScriptTM II reverse transcriptase (Invitrogen, CA, USA) and Oligo dT primers. Complementary DNA was amplified by real-time quantitative polymerase chain reaction (PCR) (TaqMan™, ABI Prism 5700 Sequence Detection System, Perkin Elmer) using fluorogenic TaqMan™ probes. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) was used as the inner standard in expression analyses of TGF-β1, TNF-α, IL-6, IL-10, MCP-1 and RANTES mRNA. All primers and probes were designed, and the assays were validated, at the Institute of

Medical Immunology, Medical University of Berlin - Charité, Germany. Because preceding experiments demonstrated amplification efficiencies in our system of nearly 1 for all panels, the specific gene expression was calculated relative to that of the housekeeping gene HPRT (comparative threshold cycle method ($2^{-\Delta cT}$)).

Genotyping of polymorphisms

The genomic DNA was isolated from whole blood samples using a commercial kit (Whole blood DNA purification kit; Fermentas, Canada). Single nucleotide polymorphisms were determined by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism method (PCR-RFLP): TGF-β1, TNF-α, IFN-γ, MCP-1, RANTES and CCR2. The insertion-deletion 32bp polymorphism in CCR5 was determined by simple PCR method.

Statistics

For comparison of data obtained in different diagnostic groups, the Mann–Whitney test with Holm's correction and the Kruskal-Wallis test were used. Expression levels were correlated with clinical and morphological data (Spearman rank correlation) and for binary variables the Mann–Whitney test was used. The ROC curve was used for setting the cutoff points of intrarenal mRNA expression levels of studied genes with the best combination of sensitivity and specificity

that indicated normal histological finding or the renal graft dysfunction in the long-term. The Kaplan–Meier survival analysis with log rank testing was used to assess renal outcome.

The Hardy-Weinberg equilibrium of alleles at individual loci was evaluated using the chi-square test. To evaluate the effect of continuous variables on the incidence of acute rejection, CAN or subclinical rejection 1 year after kidney transplantation, one-way ANOVA was used. Single-locus association analyses were performed by univariate logistic regression analysis using SPSS version 14.0 (SPSS inc., Chicago, IL, USA). Subsequently, multivariate regression adjusted for total number of mismatches, mismatches in DR locus and immunosuppression regimen was performed. For haplotype analysis, univariate logistic regression was used.

RESULTS

TGF-β1 mRNA expression

TGF-β1 mRNA expression in all kidney allografts was quantified by real-time RT-PCR. Comparisons among groups with different histological findings are shown in Figure 1. We detected a low degree of expression of TGF-β1 mRNA in kidney allografts with a normal histological pattern of renal tissue. The receiver-operating characteristic (ROC) curve analysis showed that TGF-β1 mRNA expression below 20 indicates normal histological findings with 70%

sensitivity and 73% specificity (area under the curve 0.75). In acute rejecting grafts, TGF-β1 was overexpressed, being 2.3 times higher than in non-rejecting controls ($P<0.001$). Moderate but significant TGF-β1 up-regulation was also found in renal grafts with borderline changes ($P<0.01$). TGF-β1 expression was enhanced 2.1 times during CAN compared with allografts with a normal morphological pattern ($P<0.001$). There was no significant difference in TGF-β1 up-regulation between grafts with AR and CAN although the levels were higher in the former one. TGF-β1 gene expression was strongly enhanced in ATN ($P<0.001$). Mild up-regulation of TGF-β1 mRNA expression was found in allografts with histologically proven CsA nephrotoxicity and with recurrence of GN ($P<0.05$). We did not observe significant differences of TGF-β1 expression levels in patients treated with CsA compared with tacrolimus-treated patients.

The influence of intrarenal TGF-β1 mRNA expression on short-term and long-term kidney graft outcome

TGF-β1 mRNA expression in graft core biopsy correlated with renal function (GFR) at the time of biopsy (Figure 2). There was no relation between intragraft TGF-β1 expression in acute rejection and short-term outcome of rejection (graft failure, steroid-resistant rejection and post-rejection creatinine levels).

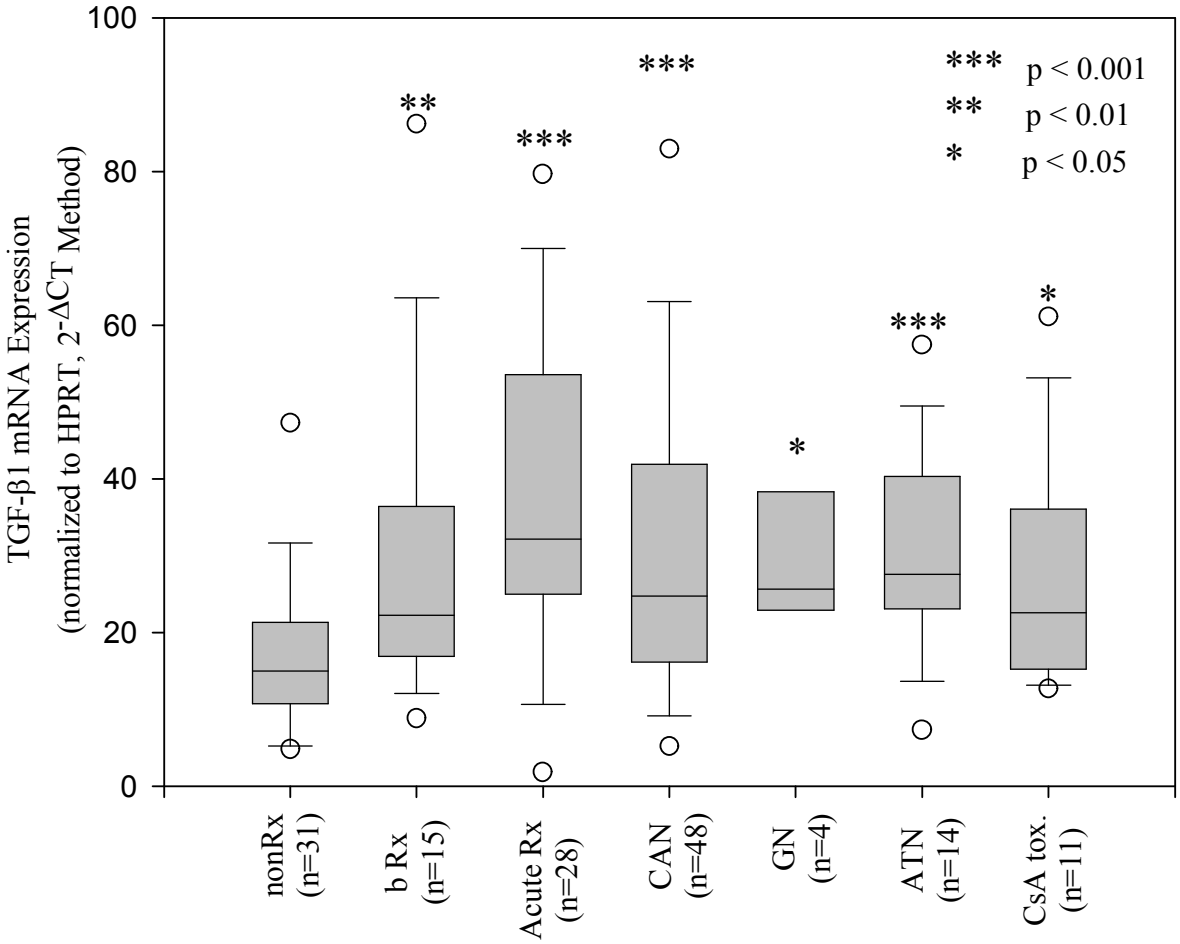

***Fig. 1*. TGF-β1 mRNA up-regulation in different causes of graft dysfunction.** *Results are expressed as ratio AU TGF-β1/ AU HPRT. The expression levels of the groups acute rejection (acute Rx, p<0.001), CAN (p<0.001), ATN (p<0.001), borderline changes (bRx, p<0.01) and Cyclosporine A toxicity (CsA tox., p< 0.05) were significantly different from the non-rejecting controls (non Rx). The box plots show 25th and 75th (boundaries of boxes), 50th (median), 10th and 90th (error bars) and 5th and 95th (dots) percentile values.*

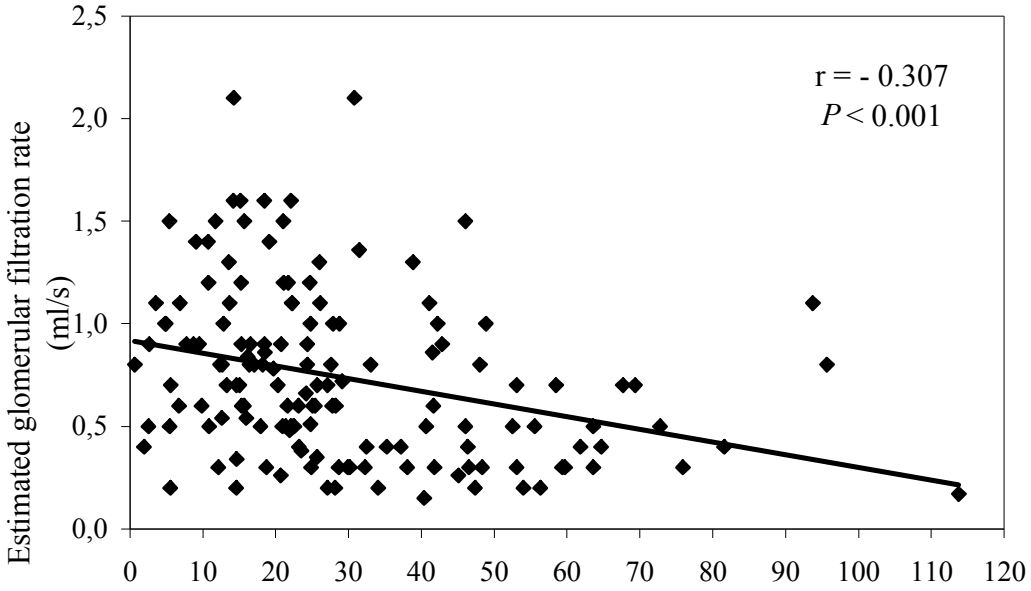

Fig. 2. The association of renal function at the time of biopsy with TGF-β1 mRNA expression. *Kidney graft function was quantified by estimated GFR.*

Renal function 18 months after the biopsy was evaluated by GFR. ROC curve analysis revealed that TGF-β1 mRNA expression over 32 was associated with deteriorated renal function 18 months after the initial biopsy (GFR < 0.8 ml/s; 77% sensitivity, 39% specificity, AUC 0.57). Enhanced TGF-β1 gene expression in the initial biopsy implied an increased risk for renal dysfunction 18 months later in patients with CAN [OR 9.9 (*P*=0.002) vs. 3.2 for low TGF-β mRNA expression]. There were insignificant trends of patients with high TGF-β1 expression towards inferior 18-months renal function in other diagnostic groups. Odds ratios are summarized in table 1.

TNF-α, IL-10 and RANTES mRNA expression

Comparisons among groups with different histological findings are shown in Figures 3-5.

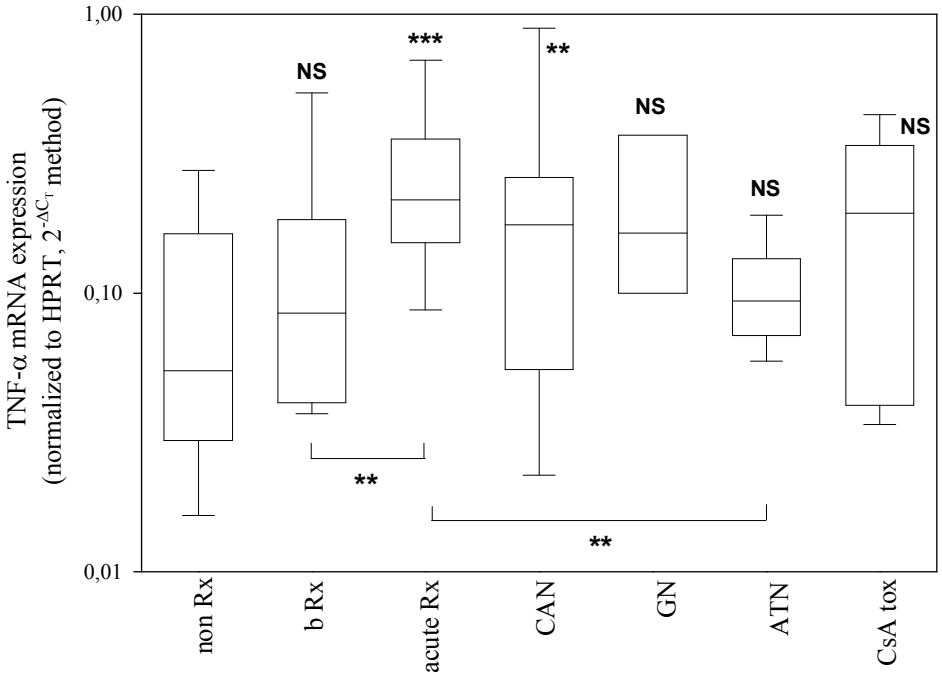

Fig. 3. TNF-α mRNA up-regulation in different causes of graft dysfunction

Patients with acute rejection and chronic allograft nephropathy exhibited significantly increased expression of TNF-α mRNA compared to non-rejecting control group (1.7 and 1.6 times higher, $P<0.001$ and $P<0.01$, respectively). TNF-α mRNA expression differed between groups of acute rejection and borderline changes and between groups of acute rejection and ATN ($P<0.01$).

Table 1. The effect of intragraft TGF-β1 mRNA overexpression on outcome. *TGF-β1 overexpression (ratio TGF-β1 vs. HPRT over 32) in initial biopsies increased the risk (odds ratio) for renal allograft dysfunction (GFR < 0.8 ml/s) 18 months later in patients with CAN.*

variable	odds ratio	95% confidence interval	*P* [a]
Non Rx, TGF-β1 ≤ 32 n = 28	1.00	-	-
Non Rx, TGF-β1 > 32 n = 3	4.20	(0.34, 52.9)	> 0.1
Borderline changes, TGF-β1 ≤ 32 n = 11	0.53	(0.09, 3.00)	> 0.1
Borderline changes, TGF-β1 > 32 n = 4	2.10	(0.25, 17.5)	> 0.1
Acute Rx, TGF-β1 ≤ 32 n = 12	2.10	(0.53, 8.41)	> 0.1
Acute Rx, TGF-β1 > 32 n = 13	3.38	(0.06, 13.3)	0.098
CAN, TGF-β1 ≤ 32 n = 30	3.17	(1.08, 9.3)	0.040
CAN, TGF-β1 >32 n = 18	9.85	(2.25, 43.2)	0.002
ATN, TGF-β1 ≤ 32 n = 9	0.60	(0.1, 3.5)	> 0.1
ATN, TGF-β1 >32 n = 5	0.53	(0.05, 5.4)	> 0.1
CsA toxicity, TGF-β1 ≤ 32 n = 8	6.30	(1.06, 37.8)	0.046
CsA toxicity, TGF-β1 > 32 n = 3	4.20	(0.74, 5.4)	> 0.1

[a] P values comes from Fisher‘s exact test

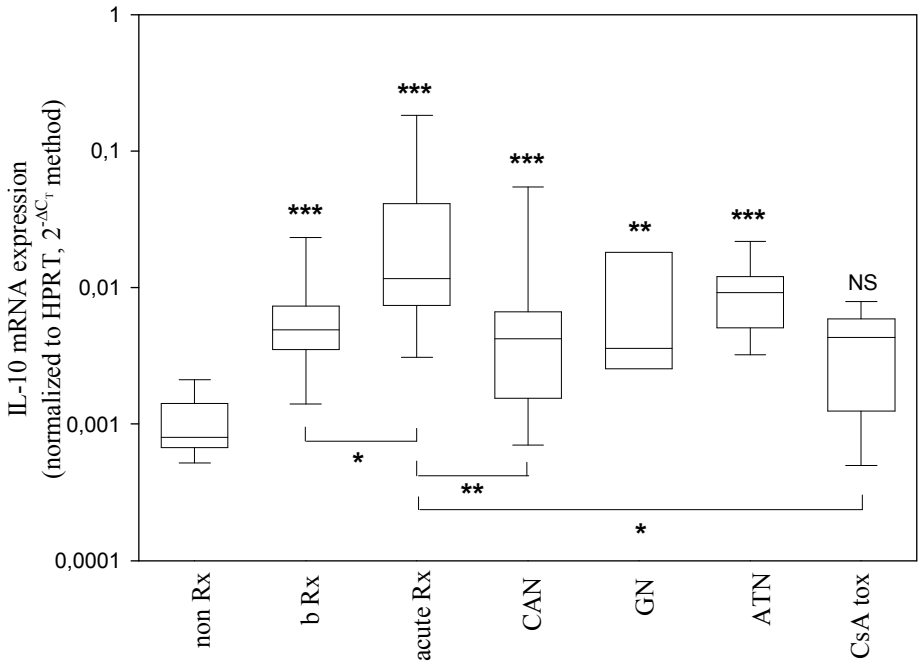

Fig. 4. IL-10 mRNA up-regulation in different causes of graft dysfunction

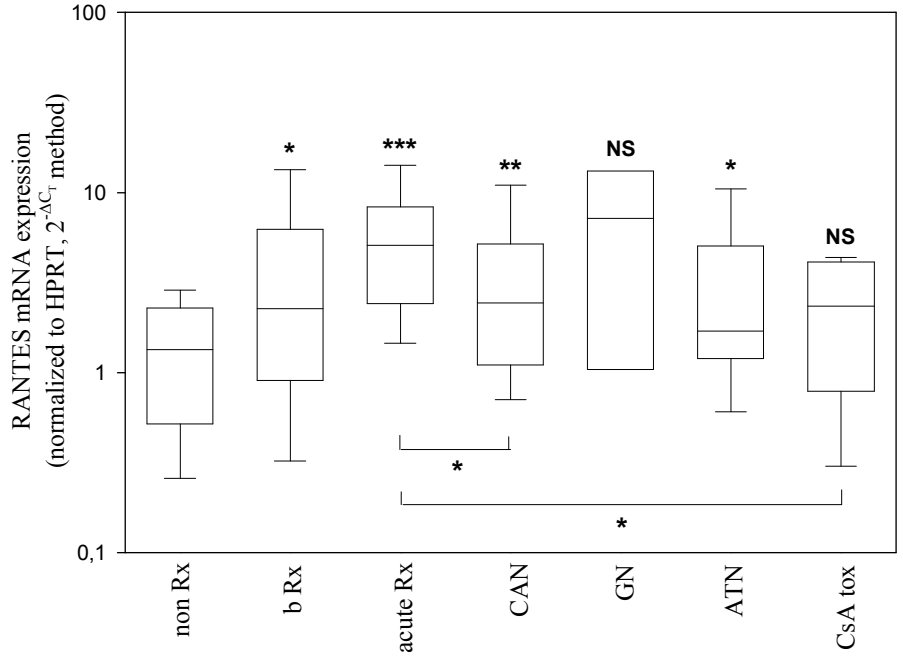

Fig. 5. RANTES mRNA up-regulation in different causes of graft dysfunction

There was very strong up-regulation of IL-10 mRNA expression in the group acute rejection (41.4 times higher then control group, $P<0.001$). Patients with borderline changes, CAN and ATN exhibited also significantly increased expression of IL-10 mRNA compared to non-rejecting control group (7.4, 13.0 and 9.3 times higher, $P<0.001$). Moderate but significant up-regulation showed group of recurrence of GN ($P<0.01$). There was significant difference between the groups of acute rejection and CAN ($P<0.01$).

Patients with acute rejection and CAN exhibited significantly increased expression of RANTES mRNA compared to non-rejecting control group (both 3.8 times higher, $P<0.001$ and $P<0.01$, respectively). Patients with borderline changes and ATN showed only moderate up-regulation of RANTES mRNA ($P<0.05$).

The expression levels of all studied genes did not differ for patients treated with cyclosporine A compared with those treated with tacrolimus.

The up-regulation levels of all studied genes during different causes of graft dysfunction are summarized in the following table 2:

Table 2: Up-regulation levels of cytokines and chemokines in kidney graft dysfunction

	TGF-β1	TNF-α	IL-10	RANTES
Borderline changes	P<0.01	NS [a]	P<0.001	P<0.05
Acute rejection	P<0.001	P<0.001 [a.b]	P<0.001 [c]	P<0.001
CAN	P<0.001	P<0.01	P<0.001 [c]	P<0.01
ATN	P<0.001	NS b	P<0.001	P<0.05
CsA toxicity	P<0.05	NS	NS	NS

[a] signifikant difference between acute rejection and borderline changes (P<0.01)

[b] signifikant difference between acute rejection and ATN (P<0.01)

[c] signifikant difference between acute rejection and CTN (P<0.01)

Intrarenal gene expression in CAN

Patients with biopsy-proven CAN exhibited significantly higher expression of all measured genes compared to the control group. The expression levels of these cytokines and chemokines were compared with clinical data of kidney graft recipients. The mRNA expression of TNF-α and RANTES correlated with the time post-transplant (P<0.05). The mRNA expression levels of almost all followed genes correlated

with proteinuria: IL-6 (P<0.001), IL-10 (P<0.01), TNF-α and MCP-1 (P<0.05). There was a trend towards higher expression of TGF-β1 and RANTES in patients with higher proteinuria.

From histomorphological parameters we found correlation between allograft tubulitis and intrarenal expression of TGF-β1, RANTES (*P*<0.01) and MCP-1 (*P*<0.05). We found increased intrarenal expression of TNF-α (*P*<0.05) in biopsies with positive C4d complement component staining (the marker of humoral rejection).

The influence of gene expression in CAN on the renal function in the long-term follow-up

Renal function 42 months after the biopsy was evaluated by GFR. ROC curve analysis in controls revealed that TNF-α mRNA expression over 0.035 (TNF-α/HPRT gene expression ratio) was associated with deteriorated renal function (GFR<0.8 ml/s) at 42 months after the initial biopsy (100% sensitivity, 60% specificity, AUC 0.78). Enhanced MCP-1 gene expression in the initial biopsy implied an increased risk for renal graft failure in CAN patients within 42 months (OR 5.1; P=0.017). Patients with CAN and enhanced intrarenal expression of TGF-β1 and MCP-1 at the time of biopsy had significantly shorter graft survival than patients with the low expression of these genes (Figure 6).

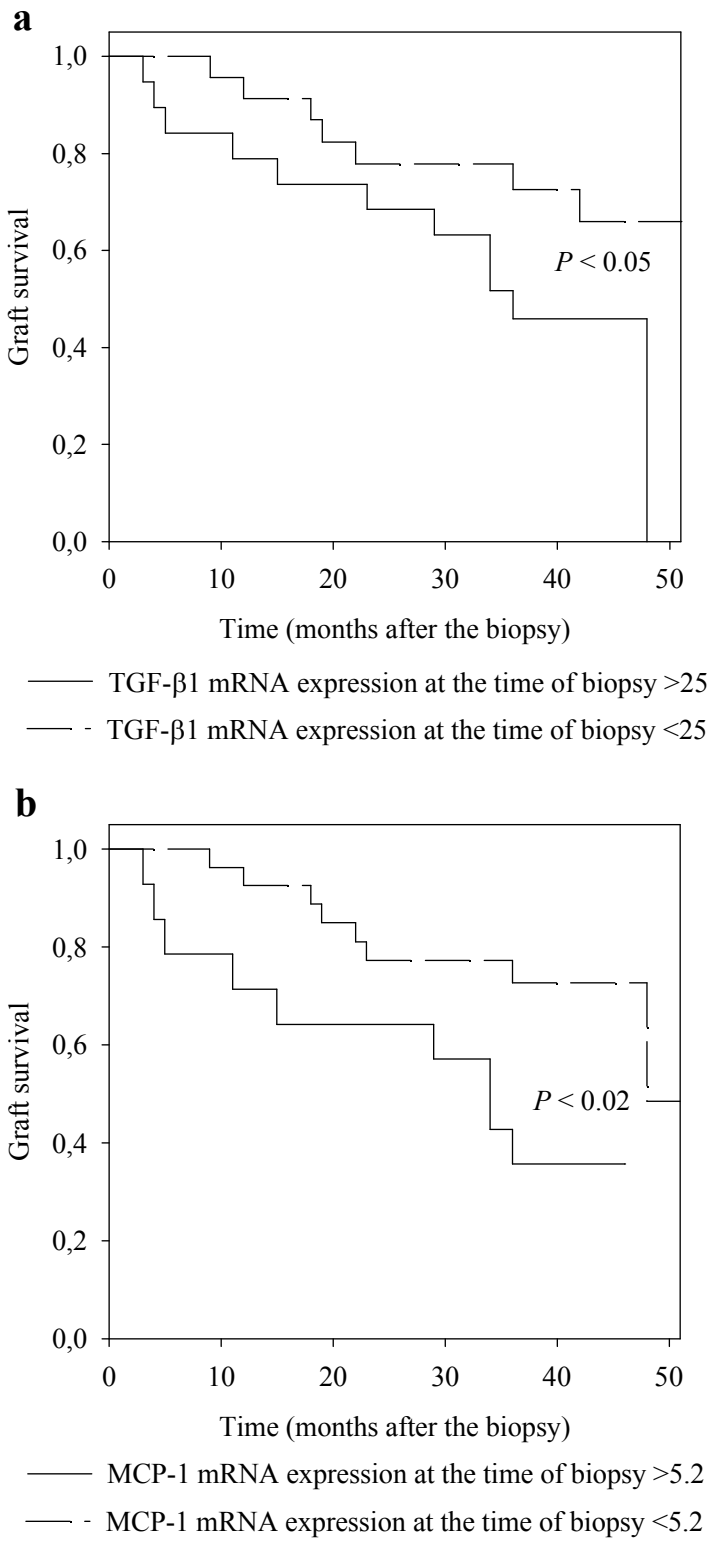

Figure 6: Kaplan-Meier analysis of graft survival in CAN patients. *(a) the influence of TGF-β1 expression (P=0,04). (b) the influence of MCP-1 expression (P=0,018).*

The influence of cytokines and chemokines genes polymorphisms on the kidney graft outcome

All alleles at individual loci were in Hardy-Weinberg equilibrium and the genotype frequencies in the control groups for all polymorphisms were in concordance with the reference HapMap database [20]. There was significant linkage disequilibrium between the TGF-β +869T/C and TGF-β +915G/C loci, with the 69% of the inferred haplotypes consisting of either T-G or C-C.

Neither univariate analysis nor multivariate analysis showed significant difference in the distribution of the genotype frequencies between patients with and without acute rejection, and between patients with CAN or subclinical rejection and individuals with normal 12-months protocol biopsy. No influence of any polymorphism on the graft survival was observed. Haplotype TGF-β [+869G; +915C] seemed to be associated with the presence of subclinical rejection (OR 3.45, 95%CI 1.19-9.99, P=0.023), but the association was non-significant due to the insufficient power.

DISCUSSION

Although the significant improvement in the one-year survival rate of renal transplants and patients has been achieved in recent decades, the fate of renal allograft has not been substantially changed in the long-term [1-3]. CAN according to the Banff 97 classification,

including IF/TA along with vasculopathy and glomerulopathy, has been shown to be present in the majority of protocol biopsies performed 12 months after transplantation [21]. Several risk factors have been identified for development of CAN, both alloantigen dependent and alloantigen independent, including the number of human leukocyte antigen (HLA) mismatches, ischemic/reperfusion injury, number and severity of rejection episodes, CMV infection, long-term CsA treatment, etc., whereby acute rejection is one of the most important of them [2]. Typical pathological features of CAN are interstitial fibrosis, glomerular changes, arterial intimal thickening and tubular atrophy [19,22].

An important inducer and regulator of fibrosis is TGF-β1 [23-25]. Its expression is up-regulated during CAN [6-8]. Although TGF-β1 expresses immunosuppressive effects by inhibiting lymphocyte activation, it also plays a proinflammatory role in tissues. Recent studies suggest that TGF-β1 may have a role in acute rejection by promoting cell-mediated cytotoxic damage [26-28]. In agreement with above-mentioned immunohistochemical studies, we confirmed enhanced intrarenal expression of TGF-β1 mRNA in acute rejection and in CAN at our cohort of patients [29-31]. Patients with up-regulated TGF-β1 mRNA expression had enhanced risk of graft failure after both acute rejection and CAN.

It has been shown that in acute rejected grafts TGF-β1, MCP-1, RANTES, MIP-1β and MIP-1α expression rise with a higher degree of tubulitis [32,33]. We found similar relation of tubulitis with the intrarenal expression of TGF-β1, MCP-1 and RANTES in CAN. This indicates different immunological activity in grafts with diagnosis of CAN, which is reflected also by different intrarenal expression levels of cytokines and chemokines. We can infer that the risk of graft failure is higher for grafts with active immunological processes than for grafts with immunologically stable disease.

Glomerular proteinuria is a risk factor for the progression of chronic renal failure and interstitial fibrosis [34-37]. Growth factors and cytokines have been shown to be translocated into proximal tubular fluid and activate tubular cells that respond with increased extracellular matrix production and chemokines secretion. It seems reasonable to hypothesize that proteinuria and growth factors ultrafiltration could cause the up-regulation of inflammatory cytokines and growth factors leading to interstitial fibrosis of the transplanted kidney. The intrarenal expression of all studied genes in CAN correlated with proteinuria. The up-regulation of MCP-1 and TGF-β1 heightened the risk for renal graft failure within 42 months and shortened the graft survival time. Based on the above-mentioned results we can recommend a tight monitoring of patients after kidney transplantation with up-regulated intrarenal

expression of pro-inflammatory genes. Proteinuria is also an important modifying factor which must require therapeutic intervention.

Cytokine and chemokine gene expression profiles are distinct among the different causes of graft dysfunction. Intrarenal expression of TNF-α in acute rejection is significantly higher than in borderline changes or in ATN. Expression of IL-10 is also higher in acute rejection than in borderline changes and it even differs from the IL-10 expression in CAN. Chemokine RANTES is more up-regulated in acute rejection than in CAN. The differences at expression levels are statistically significant, but the ranges of measured values are huge (especially in the CAN group). It makes impossible to use cytokine and chemokine expression analysis to diagnose the different causes of graft dysfunction.

Possible utilization of gene expression analysis thus resides in identifying grafts with enhanced immunological activity which are at higher risk of graft function deterioration and failure.

Analysis of cytokine and chemokine gene polymorphisms could help to find kidney graft recipients predisposed to higher cytokine or chemokine gene expression and thus predisposed to higher risk of graft dysfunction. Recently, the role of these polymorphisms in the susceptibility to the allograft nephropathy in humans has been studied and several groups reported an association with acute and chronic kidney graft rejection. However, their results are often questionable and

in some cases also dissimilar. [38-41]. Additionally, the results of studies that analysed the influence of cytokine and chemokine gene polymorphisms on the kidney allograft survival are different [42-44]. In our study, drawn up to fulfil demands of the sufficient power of tests, no association of TNF-α-308G/A, MCP-1-2518A/G, RANTES-403G/A, -109T/C, -28C/G, CCR2+190G/A, IFN-γ+874A/T, TGF-β1-869T/C, +915G/C and CCR5Δ32 polymorphisms with neither acute rejection or subclinical rejection nor CAN was found.

CONCLUSIONS

In this submitted dissertation, the results of studies performed in Transplant Laboratory and Department of Nephrology, Transplant Center, Institute for Clinical and Experimental Medicine, dealing with the influence of intrarenal expression of some cytokines and chemokines and polymorphisms of their genes on the kidney transplantation outcome, are summarized. The studies were supported by the Internal Grant Agency of the Ministry of Health, Czech Republic (Grant no. NM-7544-3) and by the Institute for Clinical and Experimental Medicine (MZO 00023001). All studies were designed to follow a large cohort of individuals in order to be able to elucidate some unclear and inconsistent published results.

1. Cytokines and chemokines TGF-β1, TNF-α, IL-6, IL-10, MCP-1 and RANTES are up-regulated in different rates in acute rejection, chronic transplant nephropathy and also in other causes of kidney graft dysfunction.
2. High intrarenal expression of TGF-β1 and MCP-1 mRNA in CAN predicts a higher risk of kidney graft dysfunction in the long-term. Also, the kidney graft survival is significantly shorter.
3. Intrarenal gene expression profile of TGF-β1, TNF-α, IL-6, IL-10, MCP-1 and RANTES is different during various causes of graft dysfunction. The intrarenal expression level cannot be used for diagnostic purposes, but it can alert higher immunological activity in kidney graft, which can lead to earlier failure of renal functions.
4. We did not confirm an association of TNF-α-308G/A, MCP-1 -2518 A/G, RANTES-403G/A, -109T/C, -28C/G, CCR2+190G/A, IFN-γ +874A/T, TGF-β1 -869T/C, +915G/C and CCR5Δ32 polymorphisms with acute rejection, subclinical rejection or CAN.

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PUBLICATION ACTIVITY:

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ORAL COMMUNICATIONS

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2. Up-regulace exprese TGF-beta v ledvinném štěpu během akutní rejekce. 5. Kongres České transplantační společnosti, Brno 2002
3. Up-regulace exprese TGF-beta v ledvinném štěpu během akutní rejekce. 29. Kongres České nefrologické společnosti, Liberec 2002
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5. Exprese cytokinů a chemokinů v lidské transplantované ledvině. 30. Kongres České nefrologické společnosti, Luhačovice 2004
6. TGF-β1 mRNA up-regulation predicts late kidney graft dysfunction. 12th ESOT Congress, Ženeva 2005

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9. Higher intrarenal cytokine and chemokine gene expression predicts earlier renal allograft failure. II. Young Investigators Forum in XII. Czech-German-Polish Symposium Heart and Kidneys and IX. One Day Conference of the Czech Nephrological Society, Liberec 2006
10. Význam exprese prozánětlivých cytokinů pro osud transplantované ledviny. Sympozium Cytokiny 2007, Praha 2007
11. Higher intrarenal TGF-β1 gene expression predicts better outcome of early acute humoral rejection of kidney allografts. American Transplant Congress, San Francisco, 2007
12. Intrarenal cytokine and chemokine gene expression in the three-months protocol biopsies. 13th ESOT Congress, Praha 2007