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# Increasing urinary IL-6 levels announce kidney graft rejection*

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**Abstract** Acute rejection (AR) is the recipient's inflammatory response to the grafted organ. Within the graft-infiltrating cells, a high ratio of IL-6 producing cells can be found, indicating local IL-6 production. Therefore, in cases of kidney transplantation, urinary (u) IL-6 should be detectable. In order to establish the dynamics and diagnostic relevance, uIL-6 levels were determined daily by Quantikine IL-6 immunoassay (R & D Systems, Minneapolis, Minn.) in 101 kidney graft recipients ($n$ = 1915 urine samples) during their post-transplant hospital stay. Immunosuppression consisted of azathioprine, steroids, cyclosporine and an intraoperative high-dose single antithymocyte globulin (ATG)-Fresenius bolus (9 mg/kg). In all the uncomplicated courses ($n$ = 31) mean uIL-6 level was determined, after a post-transplant peak of 174 pg/ml, to be between 4 and 8 pg/ml. In contrast, delayed graft function ($n$ = 16) was always associated with very high uIL-6 levels ( > 200 pg/ml), dropping down only with commencement of graft function. Steroid-sensitive AR ($n$ = 14) was consistently associated with significantly increasing uIL-6 levels prior to antirejection therapy (from 23 to 82 pg/ml). In cases of steroid-resistant AR, following antirejection therapy with methylprednisolone (5 days 5 mg/kg), there was no obvious trend towards normalization, indicating the persistence of inflammation (mean uIL-6 peak prior to OKT3 or ATG therapy: 99 pg/ml). In addition, AR-associated uIL-6 levels were found to be of much greater diagnostic relevance than AR-associated serum IL-6 levels. In bacterial urinary tract infections ($n$ = 20), increased uIL-6 levels (peak 53 pg/ml) coincided with the commencement of antibiotic therapy. In mild cytomegalovirus diseases ($n$ = 8), the development of leukocytopenia was associated with a slight increase of uIL-6 (peak 26 pg/ml), showing graft involvement. All increased uIL-6 values returned towards baseline after successful treatment. Thus, uIL-6 provides information about the intragraft inflammatory situation. Its determination is simple, expressive, non-invasive and can be recommended.

**Key words** IL-6 · Kidney transplantation · Rejection · Urinary tract infection · Cytomegalovirus disease

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## Introduction

It is generally accepted that acute kidney graft rejection (AR) is mainly mediated by mononuclear cells infiltrating the graft. In some recent investigations, polymerase chain reaction clearly showed that mRNA for IL-6 was present in renal biopsies from acute rejecting kidneys [5, 9]. In irreversibly rejected kidneys, Merville et al. [10] described a large number of IL-6 producing cells within the graft infiltrating cells (GIC; mean = 17,114/$10^6$ GIC). Some other investigators concluded from their studies that serial measurements of IL-6, in particular in urine, may be of value in monitoring renal transplant recipients [1, 2, 14, 15]. However, Newstead et al. [12] found no differences in the urinary IL-6 levels (uIL-6) between acute cellular rejection, acute tubular necrosis and chronic vascular rejections. Waiser et al. [15], describing uIL-6 as a sensitive indicator of rejection, found a reduced specificity by infection, acute tubular necrosis and antithymocyte globulin (ATG) treatment. A marked increase in uIL-6 was also oberved in patients with urinary tract infections (UTI), [3, 13) or with active lupus nephritis [4].

In this study we investigated the pattern of uIL-6 levels in 101 patients submitted to kidney transplantation (KTx) in order to clarify the usefulness of serial uIL-6 determinations in diagnosing AR. Values were also recorded in patinets undergoing antirejection therapy or infectious episodes. The results were compared with levels of serum IL-6 and creatinine.

## Materials and methods

### Study population

A total of 101 recipients [mean age 45.2 ± 10.5 years, 35 females (34.7%), 66 males (65.3%)], who underwent cadaveric renal transplant (first: 88, second: 13) between February 1993 and January 1994 at the Kidney Transplant Center Berlin-Friedrichshain, were included in this retrospective study.

### Immunosuppressive protocol

All recipients received 4 mg/kg azathioprine (AZA) in their dialysis unit immediately before being called to the transplant center. Post KTx they received 40 mg methylprednisolone (MP) for 7 days, subsequently switching to 35 mg/kg prednisolone for 14 days. After further reduction, the maintenance dose was 10–15 mg/day. AZA was restarted after surgery at a dose of 1 mg/kg orally. Oral cyclosporine (CyA) was started within 24 h of surgery. A maintenance CyA level of 100 ng/ml (radioimmunoassay, Incstar, Stillwater, Minn.) during the 1st postoperative week and 200 ng/ml thereafter was aimed for. In addition, all recipients received the Friedrichshain variant of ATG induction therapy, details of which have already been published [7, 8]. Briefly, this induction consisted of an intraoperative high-dose single ATG bolus (e.g. ATG Fresenius 9 mg/kg bw) in the operating theater before completion of anastomoses (i.e., removal of clamps). To avoid a cytokine release syndrome, 500 mg MP was administered about 1 h prior to ATG.

### Monitoring for rejection and infection

For the diagnosis of rejection, the following clinical and laboratory signs were decisive: enlargement and tenderness of the graft, increase in serum creatinine and C-reactive protein, concomitant change in blood urea nitrogen, oliguria, immunoglobulinuria, sonographic changes and immunoactivation in fine-needle aspiration cytology [6]. The treatment consisted of 5 mg/kg bw MP for 5 consecutive days. Attempts to reverse biopsy-proven MP-resistant rejections were carried out by ATG using a dose-by-T-cell protocol (aspired values: 50–150 T cells/µl). The relative number of T cells (CD $3^+$) was determined by flow cytometry (FACScan, Becton Dickinson, Heidelberg) using DIANOVA (Hamburg) monoclonal antibodies (abs). OKT3 (10 days 2.5 mg; CILAG, Sulzbach) was given as rescue therapy or primarily in cases of humoral/vascular rejections. Humoral rejection crises were proven by the detection of donor-reactive lymphocytotoxic complement dependent abs (DRA) using cryopreserved (liquid nitrogen) donor spleen lymphocytes as target cells.

Serological diagnosis of cytomegalovirus (CMV) infections was done by the detection of CMV-specific IgM (seroconversion) and/or IgG abs ( ≥ fourfold rise in titer or doubling of arbitrary units; January–November 1993: CMV ELISA Enzygnost, Behring, Marburg; December 1993 onwards: IMx CMV IgM and IgG, Abbott, Wiesbaden). CMV disease was diagnosed using clinical criteria including leukocytopenia, spike-like fever, elevation of aminotransferases, thrombocytopenia, deterioration of graft function, etc. The treatment of CMV disease depended on the severity of clinical symptoms and included the application of human immunoglobulins with a high content of CMV-specific abs (Cytotect, Biotest, Dreieich.) and/or ganciclovire (Syntex, Aachen) as well as the cessation or dose reduction of AZA.

For microbiological studies an aliquot of urinary sediment (from 10 ml urine) was inoculated into the appropriate medium (blood and McConkey agar plates) and colonies were counted 24 h later. The diagnosis of bacterial urinary tract infection (UTI) was based on the presence of at least $10^5$ colony-forming units of micro-organisms per milliliter in urine culture.

### Detection of IL-6

IL-6 levels in serum and urine were determined by the Quantikine IL-6 immunoassay (R & D Systems, Minneapolis, Mass.) according to the instructions of the manufacturers. Serum for IL-6 assay was taken before transplantation and three times a week thereafter (always between 7.00 and 8.00 a.m.) up to discharge and also after rehospitalization. Urinary samples were collected daily from the patients. A 10-ml portion of the 24-h urine sample was alkalized by sodium hydroxide after checking with litmus paper, and centrifuged at 3500 U/min for 10 min. The supernatant was taken for IL-6 determination. IL-6 quantification in serum and urine was done either immediately or after storing at –20 °C, but for no longer than 2 weeks.

### Study design

After finishing the study we divided our patients according to their post-transplant course into five groups. In order to get insight into the post-transplant dynamics of uIL-6 excretion we evaluated the

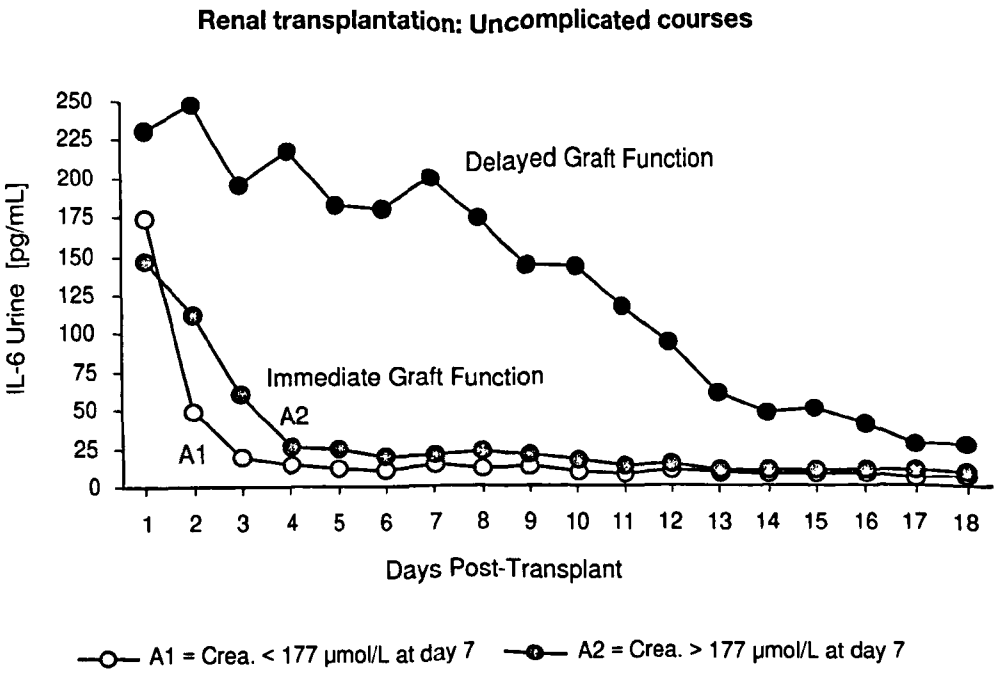


**Fig. 1** Post-transplant dynamics of IL-6 excretion in immediate and delayed kidney graft function (*Crea* creatinine)

data of recipients with immediate ($n = 31$) as well as delayed ($n = 16$) graft function, but without any other complication. In the second part we looked for patients with only one post-transplant complication, e.g. steroid-sensitive ($n = 14$) and steroid-resistent ($n = 10$) rejections, CMV disease ($n = 8$) and urinary tract infections ($n = 20$).

## Results

### Urinary IL-6 according to post-transplant graft function

Figure 1 shows the behavior of post-transplant uIL-6 excretion in kidney graft recipients with immediate (no dialysis needed) or delayed graft function but no additional complication. Patients with *excellent functioning kidney grafts* who had serum creatinine levels lower than 177 µmol/l at post-KTx day 7 (group A1, $n = 15$) were characterized by a rapid decrease of uIL-6 concentration, with a mean value less than 20 pg/ml by day 3. *In a second group of patients with immediate graft function* (group A2, $n = 16$) but a serum creatinine level at day 7 greater than 177 µmol/l, the mean uIL-6 level dropped below 20 pg/ml only by day 10. In contrast to these two groups, patients with *delayed graft function* ($n = 12$) had very high uIL-6 levels. Only with the commencement of graft function did the uIL-6 level start to drop day by day.

### Urinary IL-6 and steroid-sensitive rejection episodes

A total of 24 recipients experienced at least one rejection episode – a rejection rate of 23.8%. As shown in Fig. 2, in 14 patients with steroid-sensitive AR, uIL-6 levels (mean values) increased continuously in the pre-rejection period from 23 pg/ml 4 days prior to therapy to 82 pg/ml on the day anti-rejection therapy began (day 8 in Fig. 2). At the same time, the mean serum IL-6 levels increased from 6 to 15 pg/ml, and serum creatinine from 221 to 289 µmol/l. After the second MP bolus of 5 mg/kg bw, prompt normalization of uIL-6 concentration was already noted.

### Urinary IL-6 and steroid-resistant rejection episodes

A different behavior of uIL-6 in ten steroid-resistant rejections is shown in Fig. 3. It is clear that uIL-6 excretion was only transiently decreased during the steroid treatment (first-line therapy) in the pre-ATG or -OKT3 phase, and had started to increase again by 2 to 3 days before histological (biopsy) and clinical diagnosis of steroid-resistant rejections was established. In contrast to steroid-sensitive AR, in the more serious steroid-resistant AR the decrease of uIL-6 levels happened only slowly after initiation of ATG or OKT3 therapy. But in a comparable way, the rejection-associated uIL-6 peaks were much stronger and more impressive than the serum IL-6 increases.

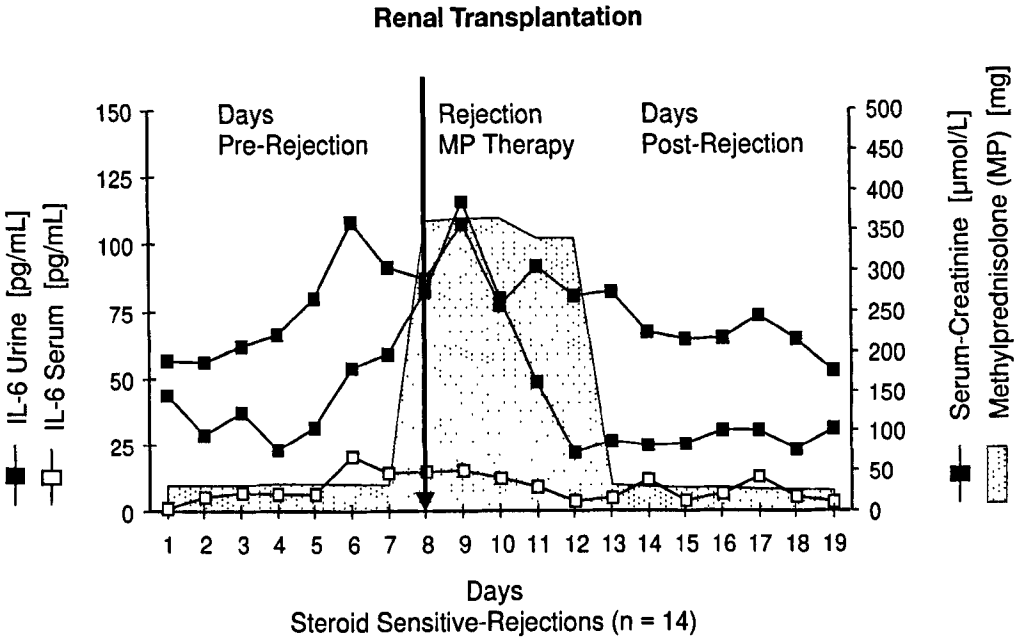


**Fig. 2** IL-6 levels in urine and serum in connection with steroid-sensitive kidney graft rejections ($n = 14$)

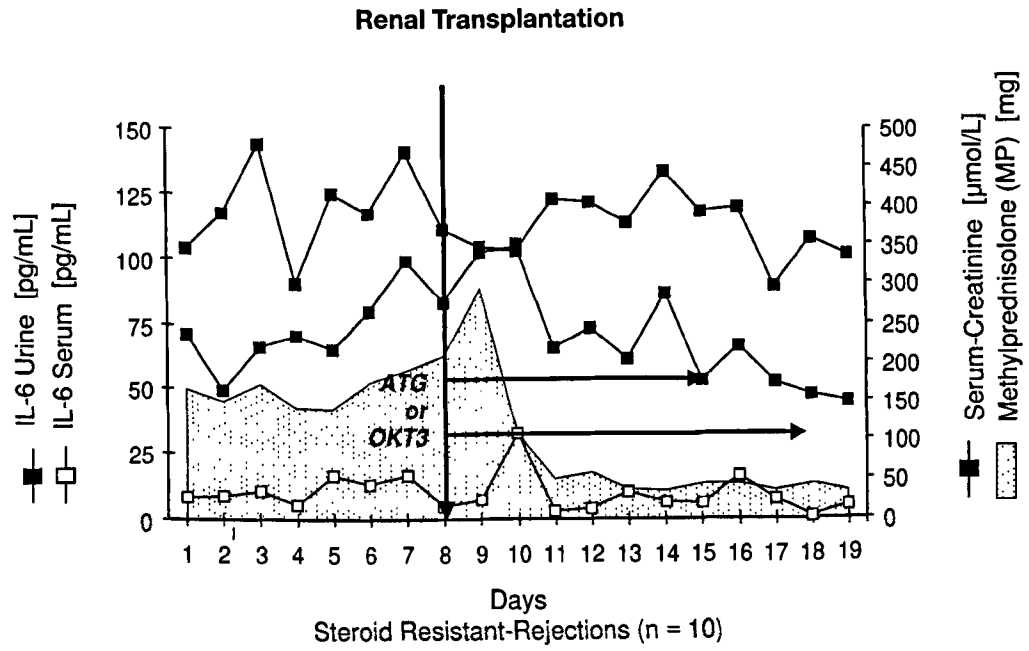


**Fig. 3** IL-6 levels in urine and serum in connection with steroid-resistant kidney graft rejections ($n = 10$)

## Urinary IL-6 and CMV disease

Figure 4 shows the uIL-6 levels in eight patients suffering from a mild CMV disease. The diagnosis was confirmed by CMV-IgM antibody detection. Leukocytopenia below 4000/µl was a common sign in all patients. In order to compare the eight individual courses, the laboratory data were arranged according to the 1st day of the leukocytopenia. In this Figure, day 8 is the 1st day of leukocytopenia in all patients. The development of this leukocytopenia was associated with a slight increase of both uIL-6 and serum creatinine levels. With regard to the uIL-6, it is worth noting that the highest mean value was only 26 pg/ml (compared with obviously higher levels in rejection crises).

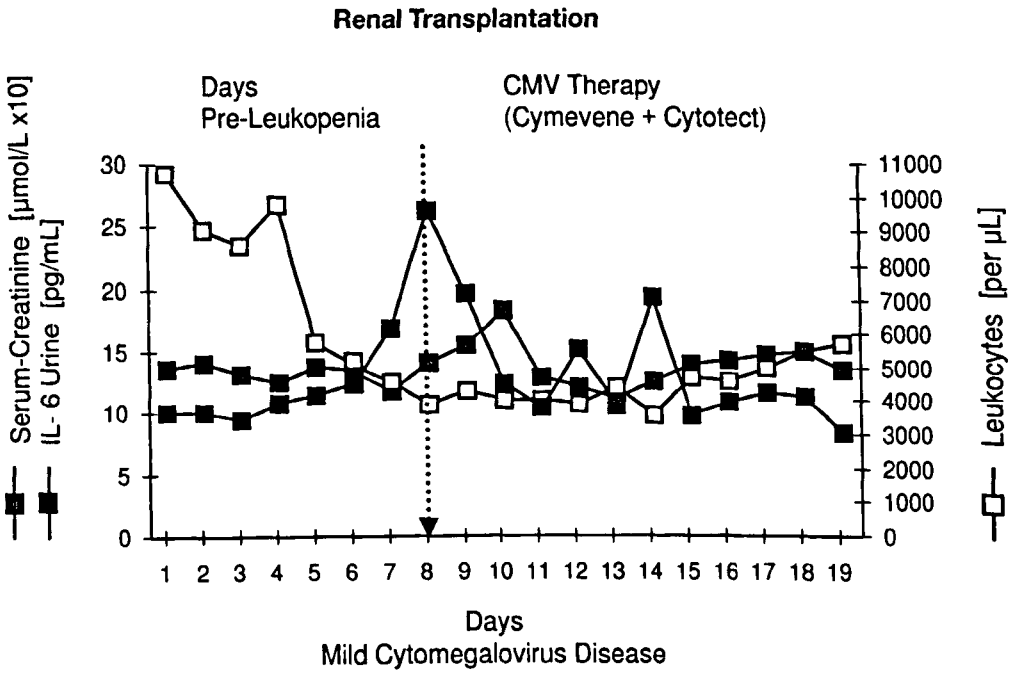


**Fig. 4** Cytomegalovirus disease associated increase of urinary IL-6 concentration in kidney graft recipients

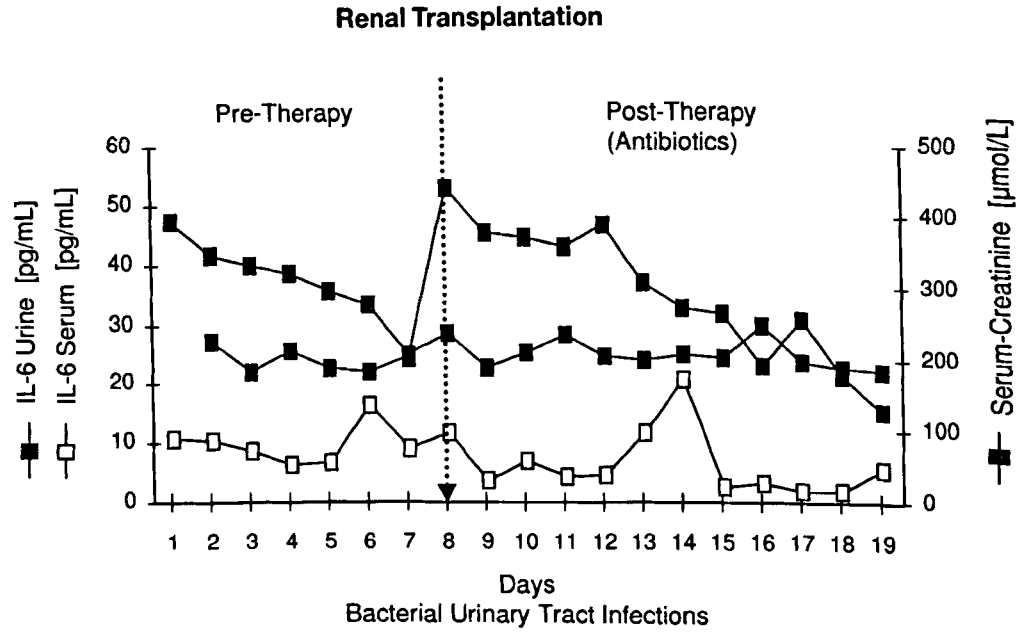


**Fig. 5** Increased urinary IL-6 level in kidney graft recipients suffering from bacterial urinary tract infection coincides with the commencement of antibiotic therapy

Urinary IL-6 and bacterial urinary tract infections

In an analogous manner, the individual uIL-6 data of 20 recipients with bacterial UTI were arranged according to the 1st day of antibiotic treatment. Figure 5 represents the mean values, and day 8 is the starting point of antibiotic treatment. Interestingly, increased uIL-6 levels coincided with the beginning of the therapy, which depended on the cultural detection of more than $\geq 10^5$ / ml bacteria in urine samples. A successful antibiotic therapy resulted in an accompanying decrease of uIL-6; after 10 days the pre-therapy values were reached again.

Urinary IL-6 in different post-transplant complications – a summary

Comparing (Fig. 6) the four different types of IL-6 curves (from Figs. 2–5), it can be said with certainty that clear increases of uIL-6 levels preceded clinical di-

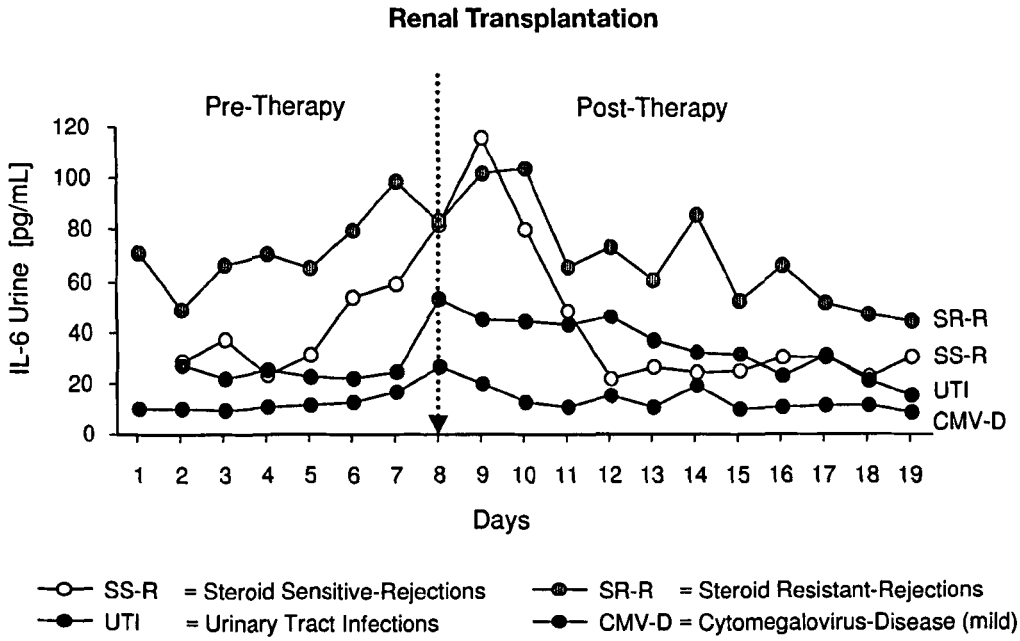


**Fig. 6** Comparison of urinary IL-6 levels in different complications after renal transplantation

agnosis of acute rejection by a mean period of about 3 days, and that ulL-6 levels also predict biopsy-proven steroid-resistant rejections. The lower urinary IL-6 peak in patients with UTI coincide with the day of cultural detection of bacteria and commencement of antibiotic therapy. The lowest peak was seen in recipients with mild CMV, indicating graft involvement in the disease. In every case, successful treatment was accompanied with decreasing uIL-6 levels.

## Discussion

IL-6 is the prototype of pleiotrophic cytokines. It is a promotor of hematopoiesis, serves as an immunoregulator of T cell growth and differentiation, induces plasma cell development, modulates bone resorption, initiates production of acute phase reactants in hepatocytes, etc. Human IL-6 is a 22–27 kDa glycoprotein expressed by a variety of cells including T and B cells, monocytes, fibroblasts, endothelial cells, granulocytes, etc.

IL-6 production is generally correlated with cell activation. Together with IL-1 and TNFα, it is one of the main pro-inflammatory cytokines. In 72 serum samples from healthy adults (C-reactive protein < 5 mg/L, HBs antigen negative, lues serology negative) the IL-6 concentration was determined by us to be between 0 and 2.82 pg/ml ($x + 3$ SD; Quantikine, R & D systems).Therefore, detectable IL-6 must be the result of its production by a variety of cell types in response to a variety of different stimuli. From an immunological point of view, the acute rejection is the recipient's inflammatory response to the grafted organ. Within the graft infiltrating cells a high ratio of IL-6 producing cells can be found, indicating local IL-6 production, e.g. by T cells and macrophages upon immune challenge. Nakamura et al. [11], investigating patients with Kawasaki disease, IgA nephropathy and renal hypoplasia concluded from the data obtained that IL-6 in renal tubular fluid may be reabsorbed and catabolized, as well as excreted, by the renal tubule, indicating that uIL-6 excretion could be influenced by both mesangial proliferation and renal tubular dysfunction. Therefore, in the case of kidney transplantation, uIL-6 should be detectable when the local production predominates over the tubular reabsorption.

In 1988, van Oers et al. [14], using a sensitive bio-assay, reported very high levels of uIL-6 on day 2 after transplantation (49.5 ± 6.6 U/ml) and 0–3 days before clinical AR (182 ± 60 U/ml). During successful antirejection therapy with MP, uIL-6 levels returned to normal within 2–3 weeks. The authors concluded from these data that serial measurements of uIL-6 may be of value in monitoring renal transplant recipients. In a small series (46 urine and 57 serum samples), Newstead et al. [12], using a home-made sandwich ELISA, found no difference in the levels of IL-6 measured in serum and urine among AR, acute tubular necrosis/CyA toxicity, and chronic vascular rejections. Casiraghi et al. [2] described an AR-associated uIL-6 increase from 121 pg/h (day –4) to 225 pg/h (day –1) before steroid therapy. Antirejection therapy resulted in prompt normalization of uIL-6. In 4/5 patients with steroid-resistant AR, uIL-6 excretion only transiently decreased during MP treatment of AR and started to increase 2–3 days before the diagnosis was established. In con-

nection with infections (7 × UTI, 3 × CMV, 1 × sepsis, 1 × epididymitis), no significant changes in uIL-6 were observed. This observation is in sharp contrast to the findings of Ohta et al. [13], who consistently detected increased amounts of uIL-6 in patients with culture-proven acute UTI. In a small series ($n = 8$ patients) Bloema et al. [1] described a markedly elevated uIL-6 excretion at the start of first and second rejection episodes. Treatment with both MP and OKT3 resulted in a decrease of uIL-6 from commencement on. With respect to the diagnostic relevance of uIL-6 for AR, Waiser et al. [15] reported a 93% sensitivity but a reduced specificity (60%), being unable to distinguish AR from infections, acute tubular necrosis or ATG treatment.

Taken together, in most reports the number of patients is relatively small (especially in certain treatment groups) and sequential (i.e. daily) examinations of uIL-6 not common. In addition, some conflicting results do exist. Therefore, we included in our study 101 cadaveric renal allograft recipients and investigated the pattern of uIL-6 on a daily basis.

In 15 patients with excellent functioning kidney grafts, characterized by a serum creatinine level lower than 177 µmol/l at post-transplant day 7, uIL-6 rapidly decreased post-KTx (peak at day 1: 174 pg/ml), falling to a mean uIL-6 value of less than 20 pg/ml by day 3. A second group of recipients ($n = 16$), with immediate functioning grafts and uncomplicated courses, but serum creatinine levels at post-KTx day 7 higher than 177 µmol/l, the mean uIL-6 level of less than 20 pg/ml was reached only at post-KTx day 10.

In contrast to these two groups, delayed graft function ($n = 12$ recipients, no additional complication) was accompanied with very high uIL-6 levels (during the first post-KTx week, between 180 and 274 pg/ml). Only in connection with the commencement of graft function did the uIL-6 levels rapidly decrease. Thus, post-transplant increased uIL-6 levels seem to reflect cellular alterations, possibly induced by cold ischemia time or other factors. In addition, the regeneration of cellular or renal function was always accompanied by the disappearance or normalization of uIL-6. This observation means that during delayed graft function uIL-6 level can not be used for detecting AR, a problem also discussed by Newstead et al. [12] and Waiser et al. [15].

Within our patient cohort, 14 out of 101 experienced steroid-sensitive and 10 steroid-resistant AR. In connection with steroid-sensitive AR we observed a significant and continuous (fourfold) increase of uIL-6 levels between 4 days prior to and the commencement of antirejection therapy with MP (from 23 to 82 pg/ml). Interestingly, the serum IL-6 levels rose at the same time from 6 to only 15 pg/ml. This means that uIL-6, but not serum IL-6, concentrations are sensitive indicators of AR. A second important finding is the prompt decrease of uIL-6 as early as after the second MP bolus of 5 mg/kg bw, reflecting the efficacy of the therapy used. Similiar observations were reported by Bloema et al. [1], Casiraghi et al. [2], van Oers et al. [14] and Waiser et al. [15]. In ten cases of steroid-resistant AR, uIL-6 excretion was only transiently decreased during MP treatment, indicating the persistence of the inflammatory process, and started to increase again by 2–3 days before the diagnosis was confirmed by biopsy. After initiation of ATG or OKT3 therapy, reduction of uIL-6 was not as rapid as that seen after MP therapy of steroid-sensitive AR. Comparing IL-6 levels in urine and serum, the uIL-6 peaks were much higher than the serum peaks in steroid-resistant AR as well.

The only data on uIL-6 and CMV infection were reported by Casiraghi et al. [2]. Two of three patients had a peak of uIL-6 (144 and 650 pg/h) on the day of diagnosis of CMV infection. We report on uIL-6 levels in eight kidney graft recipients suffering from a mild CMV disease. In all recipients the development of a leukocytopenia of less than 4000/µl (as the first sign of CMV disease) was associated with a slight increase of both uIL-6 and serum creatinine, but the highest mean uIL-6 value was only 26 pg/ml, compared with obviously higher uIL-6 levels prior to AR. This observation is further evidence for involvement of the renal graft in CMV disease.

The association of uIL-6 and UTI is hotly debated. In kidney graft recipients, Waiser et al. [15] described a reduced specificity of uIL-6 for detecting AR caused by infection, but Casiraghi et al. [2] observed no uIL-6 peaks in patients with infectious episodes. We were able to evaluate the data of 20 kidney graft recipients with bacterial UTI. All patients were treated with antibiotics on the basis of culture-proven bacteriuria. At that time no other complication was detected. Interestingly, the increase of uIL-6 levels coincided with the commencement of the therapy, but did not precede it. Successful antibiotic therapy resulted in an accompanying decrease of uIL-6; the mean pre-therapy value was reached again after 10 days.

In summary, our data show that meaningful immunological monitoring of kidney allograft recipients may be achieved by careful sequential examination of uIL-6 levels. An additional advantage is that the analyses may be be performed daily with minimal patient discomfort and without invasive procedures. All data show that uIL-6 level is a sensitive indicator of AR as well as of the efficacy of antirejection therapy. It seems also clear that the specificity is lower than the sensitivity for detecting AR, but from an practical point of view the diagnosis of AR is always made in the context of all clinical and laboratory paramenters available. Beside this, we found typical uIL-6 patterns associated with various types of complication. Because uIL-6 determination is simple, expressive and non-invasive, we can recommend it.

## References


1. Bloema E, Ten Berge IJM, Surachno J, Wilmink JM (1990) Kinetics of interleukin 6 during OKT3 treatment in renal allograft recipients. Transplantation 50: 330–331
2. Casiraghi F, Ruggenenti P, Noris M, Locatelli G, Perico N, Perna A, Remuzzi G (1997) Sequential monitoring of urine-soluble interleukin 2 receptor and interleukin 6 predicts acute rejection of human renal allografts before clinical or laboratory signs of renal dysfuction. Transplantation 63: 1508–1514
3. Hedges S, Anderson P, Lidin-Janson G, De Man P, Svanborg C (1991) Interleukin-6 response to deliberate colonization of the human urinary tract with gram-negative bacteria. Infect Immun 59: 421–427
4. Iwano M, Dohi K, Hirata E, Kurumatani N, Horii Y, Shiiki H, Fukatsu A, Matsuda T, Kishimoto T, Ishikawa H (1993) Urinary levels of IL-6 in patients with active lupus nephritis. Clin Nephrol 40: 16–21
5. Jeyarajah DR, Kadakia RA, O'Toole K, Newell KA, Josephson MA, Spargo BH, Woodle ES, Thistlethwaite Jr JR (1995) Changes in urinary cytokine mRNA profile after successful therapy for acute cellular renal allograft rejection. Transplant Proc 27: 887–889
6. Kaden J, Strobelt V, Oesterwitz H, Groth J, May G, Eichler C (1987) Monitoring of renal allograft rejection with fine needle aspiration biopsy and serum C-reactive protein determinations. Transplant Proc 19: 1657
7. Kaden J, May G, Schönemann C, Müller P, Groth J, Seeger W, Seibt E, Henkert M, Lippert J (1992) Effect of ATG prophylaxis in sensitized and non-sensitized kidney graft recipients. Transplant Int 5 [Suppl 1]:75–78
8. Kaden J, Strobelt V, May G (1998) Short and long-term results after pretransplant high-dose single ATG-Fresenius bolus in cadaveric kidney transplantation. Transplant Proc 30: 4011–4014
9. Krams SM, Falco DA, Villanueva JC, Rabkin J, Tomlanovich SJ, Vincenti F, Amend WJC, Melzer J, Garovoy MR, Roberts JP, Ascher NL, Martinez OM (1992) Cytokine and T cell receptor gene expression at the site of allograft rejection. Transplantation 53: 151–156
10. Merville P, Pouteil-Noble C, Wijdenes J, Potaux L, Touraine J-L, Banchereau J (1993) Cells infiltrating rejected human kidney allografts secrete IFN-Gamma, IL-6 and IL-10, and are modulated by Il-2 and IL-4. Transplant Proc 25: 111–113
11. Nakamura A, Suzuki T, Kohsaka T (1995) Renal tubular function modulates urinary levels of interleukin-6. Nephron 70: 416–420
12. Newstead CG, Lamb WR, Brenchley PEC, Short CD (1993) Serum and urine IL-6 and TNF-α in renal transplant recipients with graft dysfunction. Transplantation 56: 831–835
13. Ohta K, Takano N, Seno A, Yachie A, Miyawaki T, Yokoyama H, Tomosugi N, Kato E, Taniguchi N (1992) Detection and clinical usefulness of urinary interleukin-6 in the diseases of the kidney and the urinary tract. Clin Nephrol 38: 185–189
14. van Oers MHJ, van der Heyden AA-PAM, Aarden LA (1998) Interleukin 6 (IL-6) in serum and urine of renal transplant recipients. Clin Exp Immunol 71: 314–319
15. Waiser J, Budde K, Katalinic A, Kuerzdorfer M, Riess R, Neumayer HH (1997) Interleukin-6 expression after renal tranplantation. Nephrol Dial Transplant 12: 753–759