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sTNF-RII: is it useful for the early diagnosis of rejection and for prognosis after renal transplantation?

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Abstract Changes in soluble tumour necrosis factor receptor II (sTNF-RII) correlate with transplant rejection, and it increases in the course of sepsis. These changes might help to identify rejection early, and thus lead to more effective treatment. Serum and urine sTNF-RII levels were measured in 70 patients during the first 3 weeks after kidney transplantation and correlated with clinical and laboratory findings. Retrospectively, three groups were identified: I. stable transplant function ($n=23$), II. at least one rejection episode ($n=38$) and III. other complications (infection or reperfusion injury) ($n=9$). The pre-operative maximum for serum sTNF-RII was 22.4 ± 10.7 ng/ml. In group I it decreased to 9.5 ± 6.7 ng/ml on day 6 after transplantation ($P<0.01$), while in group II sTNF-RII serum levels were significantly higher on day 6 (24.9 ± 15.0 ng/ml, $P<0.01$). High levels of sTNF-RII in serum (>40 ng/ml for at least 2 days) predicted a higher risk of an unfavourable outcome. High serum levels of sTNF-RII are not specific but seem to be a prognostic indicator of a complicated course; sTNF-RII in urine has no diagnostic value.

Keywords Soluble TNF-receptors · sTNF-RII · Transplant rejection · Kidney transplantation Prognostic factors

Introduction

During the early phase after kidney transplantation, rejection is the most frequent cause of transplant loss. The differential diagnosis of transplant dysfunction includes rejection, reperfusion or pharmaceutically induced injury, and transplant dysfunction due to systemic infections or circulatory problems. The diagnosis of rejection is based on clinical parameters (reduced urine production, (sub)febrile temperature, organ swelling or pain on palpation of the transplant), on laboratory changes (increase in creatinine, leukocytosis), ultrasonographic findings (increase in arterial resistance in duplex sonography) and radiological examinations (vascular rarefaction on angiography, decrease in perfusion and function on scintigraphy). Premonitory laboratory findings are a relative increase in lymphocyte count and an increase in the ratio of T-helper to T-suppressor cells. A risk factor for early rejection is ischaemic injury of the transplant with primary anuria. Especially in the period of primary transplant non-function, the differential diagnosis of rejection is difficult.

The gold standard for the diagnosis of rejection is renal biopsy. It is a well-established procedure, but it is tedious and has a low but still considerable complication rate. Biopsy cannot be performed frequently.

Early and reliable diagnosis of rejection enables treatment to be started. Effective treatment can achieve a high rate of organ function with minimal risk, as early recognition of patients who are prone to develop infection or rejection might lead to early modification of the therapeutic modalities.

As a mediator of cytotoxic events, TNF-α plays an important role in the development of transplant rejection [8, 14, 37]: with the activation of immunologically competent cells and release of the cytokines TNF-α and interleukin (Il)-1 from macrophages there is induction of endothelial cell activation and expression of adhesion molecules and MHC-antigens. TNF-α mediates inflammatory reactions, induces apoptosis and is a growth factor for fibroblasts [24, 34], thus promoting transplant vasculopathy [32]. Together with cytokines derived from lymphocytes (Il-2 and interferon (IFN)-γ) it mediates tissue inflammation and leukocyte infiltration [16].

TNF-α hence seems to be an appropriate marker for the early diagnosis of rejection. Clinical studies have given conflicting results as regards the association of TNF-α and rejection ([15, 28] contra; [14, 19, 26] pro). The determination of TNF-α is difficult, especially when it is ligated to soluble TNF-receptors (sTNF-Rs) [7, 12].

The release of sTNF-Rs is stimulated by TNF-α. Endogenous sTNF-receptor concentrations are an indicator for the activation of the TNF-α/TNF-receptor-system [5, 8, 37] and an expression of the T-helper-cell type 1 (Th1) immuno-response, this being the reaction that mediates the cellular rejection [29, 35]. Soluble TNF-Rs may serve as indicators of the activation of the immuno-system, and because of their longer half-life their assay in body fluids is much easier and more reliable than the assay of TNF-α.

TNF-RI is detected on nearly all kinds of cells [36], while TNF-RII is found especially on lymphocytes and macrophages [4]. Owing to proteolytic processes these TNF-Rs are released into the plasma and can be detected there. Studies on liver-, heart- and kidney-transplant patients indicate that there is a correlation between a rise in TNF-RII levels and rejection [22, 31].

Material and methods

Seventy consecutive kidney transplant recipients were examined prospectively. The indication for kidney transplantation was chronic renal failure on dialysis. All grafts were cadaver kidneys. Immunosuppression was started as triple drug therapy (azathioprine, prednisolone and cyclosporin) with prednisolone 20 mg/day for at least the 1st 3 weeks.

Clinical and laboratory examinations were performed to check transplant function and cyclosporin levels daily, and to screen for infections (wound swabs twice a week, CMV-PCR in blood and urine once a week, daily urine testing, daily clinical examination and, if necessary, chest X-ray and bronchoscopy for diagnosis of pneumonia).

Depending on the clinical and laboratory findings, diagnostic screening was extended to include transplant biopsy, angiography, scintigraphy or MRI to distinguish between the causes of transplant dysfunction. Serum and urine sTNF-RII levels were monitored daily during the 1st 3 weeks. Further clinical and laboratory controls of health status and transplant function were done at least at 3, 6 and 12 months post-operatively. sTNF-RII levels in serum and urine were checked at these times. Ten millilitres of venous blood were taken before breakfast and processed within 30 min. The serum was stored at –70 °C until required for examination.

Urine sTNF-RII levels were measured in early morning urine. sTNF-RII was determined by the EASIA technique (Medgenics Diagnostics, Biosource Europe). Control groups were non-transplanted healthy volunteers ($n = 44$).

Diagnosis of rejection was established on the basis of clinical and laboratory findings supplemented by duplex sonography and histology (interstitial or vascular infiltrates, endotheliitis). For study reasons, some patients were given anti-ICAM antibodies for rejection prophylaxis ($n = 12$) for the 1st 5 postoperative days. All patients showing rejection were given a high-dose corticosteroid course (1,000 mg Soludecortin/day i.v. for 3 days then slowly decreasing). In the event of a steroid-resistant rejection, treatment was continued with a polyclonal T-lymphocyte antibody (ATG, Fresenius, Germany) or if this failed, with a monoclonal antibody (OKT3, Cilag, Germany).

The diagnosis of infection was based on clinical signs (fever, malaise, signs of sepsis) with evidence of a septic focus, positive bacterial culture or viruses in PCR.

sTNF-RII values were retrospectively correlated to the following clinical situations:

- Group I. Stable transplant function.
- Group II. At least one rejection episode during the first 3 weeks after transplantation.
- Group III. Transplant dysfunction due to other causes (e.g. primary transplant non-function, infection, cyclosporin toxicity).

Statistical analysis was done by the Mann-Whitney U-test, for quantitative features, and by the chi-square-test, for qualitative features. Statistical significance was taken as $P < 0.05$.

Results are expressed as means ± standard deviation (SDs).

Results

Group I comprised 23 patients; group II, 38; and group III, nine patients. The sTNF-RII levels of healthy non-transplanted volunteers ($n = 44$) were 4.3 ± 0.7 ng/ml in serum and 7.7 ± 5.1 ng/ml in urine, and in patients with renal insufficiency on dialysis they were 22.4 ± 10.7 ng/ml in serum and 35 ± 40 ng/ml in urine, provided there was still some output of urine (before transplantation, $n = 20$).

Rejection episodes occurred between a few hours and up to 15 days after transplantation; on average 5 days after transplantation. Comparison of groups I and II showed that there was already a decrease in serum sTNF-RII levels a few days after transplantation in group I (Fig. 1) (13 ng/ml on day 3), significantly lower ($P < 0.05$) than in group II (22 ng/ml). After 6 days the serum levels in group I were 9.5 ± 6.7 ng/ml, and in group II 24.6 ± 15 ng/ml ($P < 0.01$). As time went on these differences became even more evident. On the days before rejection, serum sTNF-RII levels were elevated to 22 to 25 ng/ml, and serum creatinine levels to 7 ± 4.4 mg/dl.

In group III sTNF-RII levels were between those of groups I and II during the 1st 5 days after transplantation, then decreased after the 1st week to levels comparable with those of group I. Group III differed significantly from group II at day 6 ($P < 0.05$), while serum creatinine at 8.1 ± 5.4 mg/dl was still elevated but did not differ from those of group II.

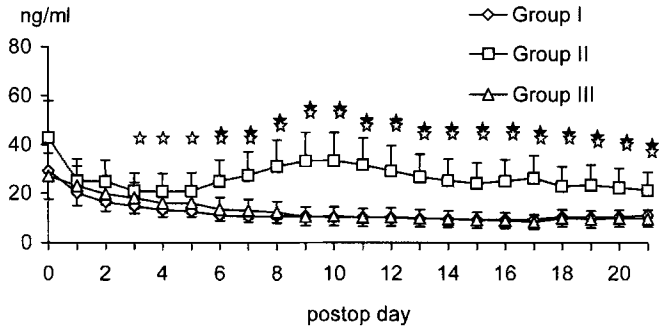

Fig. 1. Serum sTNF-RII after transplantation. Comparison between normal course (*Group I*), rejection (*Group II*) and transplant dysfunction from other causes (*Group III*). After 3 days serum levels in group I and group II are significantly ($P < 0{,}05$) different, while group III and group II are significantly different only after 6 days post-transplantation

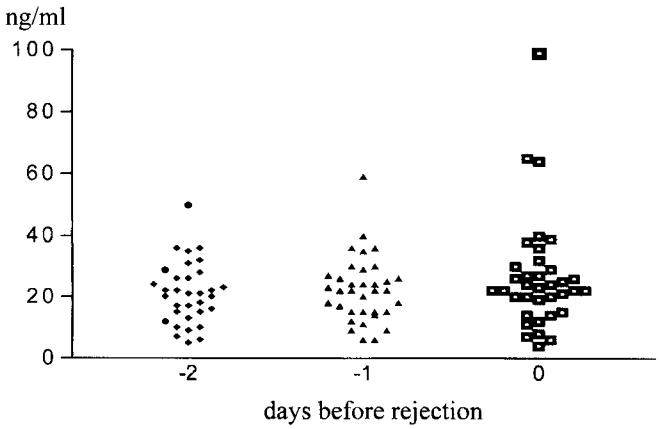

Fig. 2. Serum sTNF-RII before rejection. The levels are approximately 20 ± 10 ng/ml 2 days before the beginning of rejection, 22 ± 11 ng/ml 1 day before the beginning of rejection and 27 ± 18 ng/ml on the day of the clinical appearance of the rejection

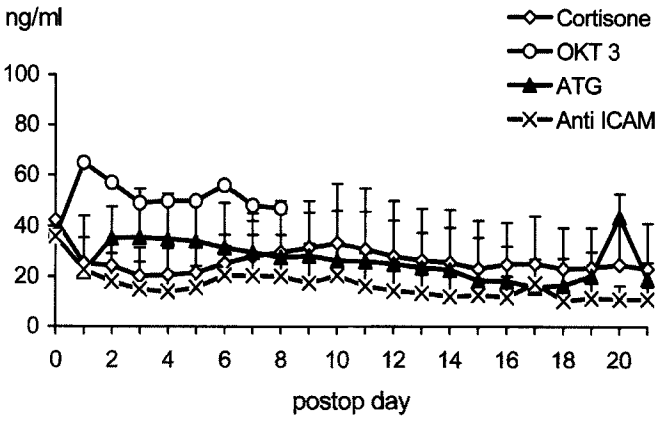

Fig. 3. sTNF-RII levels and therapy. Anti-ICAM ($n = 12$), high dose corticosteroids ($n = 29$), ATG ($n = 21$) and OKT3 ($n = 1$)

If sTNF-RII levels were corrected for renal function (sTNFR-II divided by serum creatinine), by the 5th post-transplantation day there were significant differences between patients with transplant rejection and those with transplant dysfunction.

Urine sTNF-RII levels were approximately 5–50 ng/ml, varying during the post-transplantation course, with no correlation to medication, rejection, infection or renal function. Urine levels of sTNF-RII in groups I, II and III were not significantly different during the 1st 3 weeks after transplantation.

Creatinine clearance had already increased in group I on the 1st post-operative day ($P < 0.05$), compared with group II. The creatinine clearance levels of group III were between those of groups I and II. There were no significant differences in creatinine clearance between group III and the other two groups. There was some correlation between serum creatinine and sTNF-RII, with a correlation coefficient of $r = 0.5$.

Serum sTNF-RII levels were increased before rejection. The levels were approximately 20 ± 10 ng/ml 2 days before the beginning of rejection, 22 ± 11 ng/ml 1 day before the beginning of rejection, and 27 ± 18 ng/ml on the day of the clinical appearance of the rejection (Fig. 2).

As regards medication, there were 12 patients receiving, on a study basis (as part of a separate multicentre trial), anti-ICAM antibodies post-operatively; 29 patients were on high-dose corticosteroids; and 21 patients were on ATG therapy for rejection. There were no significant differences in sTNF-RII levels in the different medication groups. Because there was only one patient receiving OKT3, no definite statement can be made (Fig. 3).

In the 1st year after transplantation there was an unfavourable outcome in nine cases: graft loss in seven patients and death in two, due to sepsis complications. These patients had very high serum sTNF-RII levels during the 1st 3 weeks after transplantation. When the sTNF-RII levels were higher than 40 ng/ml for at least 2 days ($n = 14$), there was a high rate of transplant loss and mortality. In the group with high sTNF-RII levels 1/14 (7%) died and six (42%) lost their transplant, while those not having levels above 40 ng/ml had a significantly ($P < 0.01$) better outcome [mortality 1/56 (2%) and transplant loss 1/56 (2%)]. The average levels of those with unfavourable outcomes and the others did not differ significantly at any day during the 1st 3 weeks, but the maximum levels reached only for a few days were higher (Fig. 4). Very high levels were found in the patient receiving OKT3 as well, and he also lost his transplant in the further course.

Discussion

TNF-α is a potent mediator of inflammatory reactions and exerts its action through two receptors: TNF-R I (55

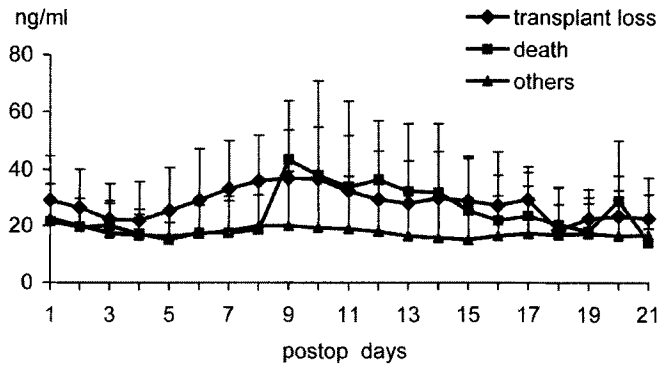

Fig. 4. sTNF-RII and prognosis. Increased sTNF-RII levels correlate with an unfavourable course

kDa) and TNF-RII (75 kDa; after proteolysis 42 kDa) [8]. Acting via TNF-RII, TNF-α stimulates the proliferation of primary thymocytes and a cytotoxic T-cell sub-population [36].

These receptors can be found in serum and urine after proteolysis. They are eliminated via the kidney. Endogenous production of TNF-α leads to release of sTNF-Rs. That means that stimulation by Il-1, Il-2 or Il-6 will increase the production of TNF-α as well as the release of sTNF-Rs. Their levels can even exceed the TNF-α levels [8, 17].

For the possible interactions between TNF-α and sTNF-R see Table 1 (modified according to Diez-Ruiz [8]).

Acting in synergy with IFN-γ and Il-2, TNF-α mediates the acute transplant rejection [11, 14, 16, 19], but methods for its detection lack reliability. sTNF-RII would seem to be the ideal marker for the diagnosis of rejection, because its assays are more reliable and its half-life is longer. TNF-RII is closely related to TNF-α [21].

As a predictor of early rejection, high levels of sTNF-RII are of limited value because of their renal elimination. Raised sTNF-RII serum levels are found in renal insufficiency and dialysis [17].

Table 1. The different possibilities of interaction between TNF-α and sTNF-R modified according to Diez-Ruiz et al. [8]

Function	Role	Interaction
sTNF-R action	Antagonist or inhibitor	Direct inhibition of TNF α at the cell surface
		Competitive binding to TNF α
	Binding protein	Removes TNF α from its place of origin
	Stabiliser	Reduces the dissociation rate of TNF α
		Reservoir for biologically active TNF α
		Prolongs TNF α effects

In summary, the value of the TNF-Rs in the diagnosis of rejection after kidney transplantation is still being debated (Leeuwenberg et al. [25] contra; Keil et al. [22] pro). There are also observations suggesting that high levels of sTNF-Rs in the course of inflammatory reaction may aggravate the clinical course and may correlate with a bad outcome [21, 31].

As sTNF-R levels are dependent on kidney function there is still debate on whether their assay is useful for transplant monitoring. Relatively high levels of sTNF-RII directly after transplantation are partly due to reperfusion injury, which causes an increase in TNF-α [33], and partly due to the recovery of kidney function [17]. Our results, as well as others' [9, 31], show that serum sTNF-RII levels are elevated after transplantation even before any clinical sign of rejection. This is partly due to a decrease in creatinine clearance, and therefore due to kidney dysfunction and decreased sTNF-RII elimination [17]. A rise in serum sTNF-RII alone is not pathognomonic of rejection after kidney transplantation.

Even when adjusted for kidney function, sTNF-RII levels are elevated when compared with serum creatinine or creatinine clearance in cases of rejection.

As early as 3 days after transplantation there are significant differences in sTNF-RII levels between patients with rejection and those with a normal course. In patients who have other causes of transplant dysfunction, sTNF-R II is significantly lower as early as 6 days after transplantation, and if corrected for kidney function, 5 days after transplantation. During the 1st 3 weeks post-operatively, the creatinine clearance was never significantly different in this group compared with those with a rejection episode. As a marker of rejection an increase in sTNF-RII levels seems useful, though with the disadvantage of being a late clue to the differential diagnosis of transplant dysfunction. These results are at variance with those of Lambert et al. [23] and Leeuwenberg et al. [25], who could find no relationship between sTNF-RII and rejection, but their results might be due to the concomitant therapy with ATG given in their studies, possibly leading to increased sTNF-RII levels primarily. Even more conflicting are the results of Dörge et al. [9], who did find a reduced release of TNF-RII during rejection, though in a rather small number of patients. Our results are in agreement with those of others [22, 27, 31] who did observe an increase in TNF-RII preceding and during rejection (liver and kidney), even though they did not take kidney function into account.

In animal models exogenous administration of sTNF-R had a beneficial effect on transplant survival while suppressing T-cell function at the same time [11].

During preclinical sepsis trials, beneficial effects were shown for both receptors [2]. sTNF-RII has been noted to have an adverse effect on the clinical course (increase of mortality in sepsis) when used for treatment of sepsis [13, 30]. Only the clinical administration of TNF-RI

seemed to give more promising results, leading to some reduction in mortality from sepsis [1].

In vivo the antagonistic effect seems to outweigh the agonistic effect of the TNF-Rs. As the endogenous increase in TNF-R expression is probably due to high TNF-α serum levels and activity, it may reflect an attempt to suppress the TNF-α effect rather than the possibility that sTNF-RII might tend to accelerate the progress of the disease. Investigations on sepsis [21], as well as after solid organ transplantation [22], showed that high sTNF-RII levels are a negative prognostic indicator. That was confirmed by this investigation, as patients with high sTNF-RII levels have a higher risk of graft loss and are at risk of sepsis complications. High serum levels of sTNF-RII seem to be a marker for poor outcome.

An increase of sTNF-RII associated with certain medication such as ATG or OKT3 has been found by other groups [3, 18, 25], but we did not observe this, probably because our medication was not the same (different dosage of ATG) and because of the small number in the OKT3 treatment group.

Further investigations may show whether these observations are still valid under the new immunosuppressant regimens (e.g. mycophenolate mofetil suppresses TNF-α release [10]).

Urine TNF-α levels are increased in rejection [20], and there is an increase in TNF-Rs on renal tubule cells [6], but levels of sTNF-RII in urine did not increase, either in cases of rejection or infection. Probably because of transplant dysfunction and interacting immunological processes there was no significant increase of urine sTNF-RII. Urine sTNF-RII levels are, therefore, without diagnostic relevance.

In summary, we can state that sTNF-RII is of limited value in the acute phase of rejection because serum levels are partly dependent on kidney function.

As a prognostic indicator any increase will point to the likelihood of an unfavourable course, indicating sepsis complications as well as high rates of transplant loss and mortality. In rejection therapy high sTNF-RII levels should prompt the clinician to search carefully for signs of infection and, if necessary, start suitable therapy. sTNF-RII determination in urine is of no value for this purpose.

The biologic role of sTNF-RII is largely unknown. As a prognostic factor, high or low levels might give hints on the further clinical course and thus help to optimise the post-operative care of transplant patients.

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