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ORIGINAL ARTICLE

Soluble BAFF Cytokine Levels and Antibody-Mediated Rejection of the Kidney Allograft

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Abstract The B-cell activating factor (BAFF) cytokine has important functions for the survival and maturation of B lymphocytes, which implies that this cytokine might play a role in the development of antibody-mediated rejection (AMR) after kidney transplantation. In our study, we compared the concentrations of the soluble BAFF cytokine in kidney graft recipients with AMR and patients without rejection with the goal of testing the hypothesis whether BAFF level measurement might be useful as a diagnostic marker of AMR. The study included a cohort of 19 high-risk patients with diagnosed AMR and 17 control patients free of rejection. BAFF was measured in all patients before transplantation, during the rejection episodes, and three months after transplantation in patients free of rejection using the Luminex technique. Before transplantation, the serum concentrations of BAFF in patients with AMR and kidney recipients without rejection did not significantly differ. After transplantation, however, BAFF levels were significantly lower in patients with AMR and also in patients with concurrent humoral and cellular rejection compared with patients without rejection ($p < 0.05$ and $p < 0.01$, respectively). No correlation was found between BAFF and the production of donor-specific antibodies (DSA) before and after transplantation. Patients experiencing AMR and simultaneous cellular and AMR had significantly lower concentrations of BAFF in comparison with patients free of rejection.

Keywords BAFF · Kidney transplantation · Antibody-mediated rejection · HLA

Introduction

Antibody-mediated rejection (AMR) is a severe immunological complication which is associated with the production of donor-specific antibodies (DSA) and, besides kidney graft failure, may impair long-term survival of transplanted organs (Colvin 2007). Recently, the role of cytokines regulating the development of B lymphocytes has been in the focus of intensive analysis. The B-cell activating factor (BAFF) is a cytokine belonging to the TNF superfamily and supports survival, maturation, and activation of B lymphocytes (Mackay and Ambrose 2003; Mukhopadhyay et al. 1999; Schneider et al. 1999). BAFF exists in two forms, as a transmembrane protein and as a soluble trimer, and its expression is enhanced by IFN-α, IFN-γ, and IL-10 (Nardelli et al. 2001; Scapini et al. 2003). In addition to the fact that BAFF is important for B-cell development, excessive production of BAFF may give rise to autoimmune diseases, such as systemic lupus

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erythematosus, B-cell hyperplasia, Sjögren's syndrome, rheumatoid arthritis, etc (Mariette et al. 2003; Ota et al. 2010; Zhang et al. 2001). As far as transplant reactions are concerned, it has been reported that BAFF might facilitate the production of DSA (Thibault-Espitia et al. 2012) and could correlate with impaired function of the kidney allograft (Mariette et al. 2003; Xu et al. 2009). High-risk patients who underwent DSA-incompatible kidney transplantation exhibited elevated concentrations of BAFF and were at increased risk of AMR; however, this correlation was not observed in antibody-compatible recipients (Banham et al. 2013). The report of Snanoudj et al. (2014) showed a positive correlation between anti-HLA antibodies and BAFF concentrations in serum, but no association with the development of AMR was found.

Given the contradictory data in the literature, the aim of this study was to compare BAFF levels between high-risk patients with diagnosed AMR and a control group of patients without rejection, i.e., to test the hypothesis whether BAFF concentrations might be useful as a diagnostic marker of AMR. In AMR patients, BAFF levels were defined before transplantation and during rejection. In the control patient group, BAFF was determined before transplantation and 3 months after transplantation.

Patients, Materials, and Methods

The research was approved by the Ethical Committee of our Institute, and, before inclusion into the study, written informed consent was obtained from all patients. Thirty-six patients who underwent kidney transplantation in our centre were included. Nineteen patients with AMR were transplanted during the period 2009–2013. Antibody-mediated rejection was diagnosed within 2 months after transplantation; patients were followed up for graft function over a period of 1 year after transplantation. Seventeen control patients were transplanted during the years 2004–2005 and had immediate development of graft function with no rejection episodes for up to 10 years after transplantation. Of the 36 recipients, 6 were transplanted with kidneys from living donors and 30 from deceased donors. Patient sera were collected 0–21 days before transplantation. In patients without rejection, measurements of BAFF were performed 3 months after transplantation, during regular check of kidney graft function, whereas in patients with AMR, BAFF levels were defined during the rejection episode (0–2 months after transplantation). No patient had primary autoimmune disease which would influence BAFF levels. In our study, only the soluble BAFF cytokine was analysed.

The levels of the BAFF cytokine were measured using the Xmap (Luminex) method (R&D Systems, Minneapolis, USA) according to the manufacturer's instructions. The minimum detectable concentration of BAFF was 0.56 pg/ml. Panel reactive antibodies (PRA) were defined by the complement-dependent cytotoxicity (CDC) test on lymphocytes collected from 50 healthy individuals. Detection of HLA antibodies by solid-phase technique was performed by the LABScreen Mixed method; positive sera in the LABScreen test were further tested for specificity by Single Antigen (SA) beads (OneLambda Inc.) according to the manufacturer's instructions. A cutoff for positivity of 1000 MFI and 2000 MFI was applied for Class I and Class II SA beads, respectively. Acute cellular rejection (ACR) and AMR were diagnosed in graft biopsies according to the updated Banff classification (Solez et al. 2008). AMR was defined by morphological evidence of acute tissue injury, immunofluorescent detection of diffuse C4d deposits in peritubular capillaries (>10%), and the presence of DSA in patient sera.

Statistical Analysis

Statistical evaluation of results was performed using GraphPad InStat 5 and MedCalc software. Age, serum creatinine, BAFF cytokine levels, and the number of HLA mismatches were analysed using the Mann–Whitney test. Gender, PRA, compatibility between the recipient and donor in the AB0 system, the number of transplantations, induction, and maintenance immunosuppression were analysed using the χ^2 test with Yates correction. Results are shown as mean ± standard deviation or percentage. Differences between the data were statistically significant when the p value was <0.05.

Results

As indicated above, the patient cohorts included 19 risk patients with diagnosed AMR (11 males and 8 females) and 17 control patients without rejection (10 males and 7 females). The mean age of the AMR group was 55 ± 6 years, while the age of the control group was 51 ± 17 years. Out of the 36 patients, six were transplanted with kidneys from living donors (five of those patients developed acute AMR), while the remaining 30 recipients received kidneys from deceased donors. All patients were transplanted for the first time. Eleven patients who were treated with induction therapy (anti-thymocyte globulin or basiliximab) were diagnosed with AMR. Applied maintenance immunosuppression was a combination of tacrolimus, sirolimus, and prednisone. Demographic and other clinical data are shown in Table 1. No significant differences in gender, age, or type of donor (living/deceased) were found between the cohorts. Patients who

Table 1 Demographic and clinical data of kidney recipients and incidence of acute antibody-mediated rejection

	No rejection		AMR[a]		*p* value
	$n = 17$	Range/(%)	$n = 19$	Range/(%)	
Recipient age ($n = 36$)	55 ± 6	(44–66)	51 ± 16	(34–82)	NS[d]
Gender					
Male ($n = 21$)	10	48%	11	52%	NS
Female ($n = 15$)	7	47%	8	53%	
Type of donor					
Living ($n = 6$)	1	17%	5	83%	NS
Deceased ($n = 30$)	16	53%	14	47%	
Serum creatinine (μmol/l)					
1-month ($n = 36$)	117 ± 32	(81–208)	260 ± 156	(109–426)	<0.0001
3-month ($n = 34$)	124 ± 30	(82–204)	185 ± 65	(99–312)	<0.01
6-month ($n = 33$)	113 ± 20	(79–159)	184 ± 106	(78–518)	<0.05
12-month ($n = 35$)	104 ± 14	(73–134)	207 ± 135	(93–614)	<0.001
Induction immunosuppression					
No ($n = 24$)	16	67%	8	33%	<0.01
Yes ($n = 12$)	1	8%	11	92%	
Maintenance immunosuppression					
FK506[b], MMF[c], Prednisone ($n = 30$)	14	82%	16	84%	NS
FK506, Rapamycin, Prednisone ($n = 2$)	0	0%	2	11%	
Cyclosporine, MMF, Prednisone ($n = 2$)	2	12%	0	0%	
Other ($n = 2$)	1	6%	1	5%	

[a] Antibody-mediated rejection

[b] Tacrolimus

[c] Mycophenolate mofetil

[d] Not significant

developed AMR had significantly higher concentrations of serum creatinine after the first ($p < 0.0001$), third ($p < 0.01$), sixth month ($p < 0.05$), and 1 year ($p < 0.001$) after transplantation (Mann–Whitney test). Furthermore, serum creatinine levels in rejecting patients were compared with the type of donor. Patients who received kidneys from living donors ($n = 5$) had significantly lower creatinine concentrations than patients with grafts from deceased donors ($n = 14$; $p < 0.05$). Among patients with AMR ($n = 19$), nine patients developed simultaneously ACR (5 males, 4 females, age 53 ± 14 years). There were no significant differences in gender, age, or application of induction immunosuppression between these patients and patients without rejection.

Selected Risk Factors in Relation to the Incidence of AMR

The number of HLA mismatches in patients free of rejection ($n = 17$, 4.3 ± 1.6) and patients with AMR (3.9 ± 1.6) were approximately the same. In addition, no major variations were found in the level of PRA before transplantation in both patient cohorts (11 patients without rejection had PRA < 10% and six had PRA ≥ 10%; in AMR patients, seven had PRA < 10% and eight had PRA ≥ 10%; Table 2).

Concerning BAFF levels, before transplantation, the serum concentrations in patients without rejection (3.5 ± 0.9 ng/ml) were higher than in patients with AMR (2.9 ± 0.7 ng/ml), however, this trend did not reach statistical significance. Conversely, after transplantation, BAFF levels in patients free of rejection were significantly higher than in patients with AMR (3.2 ± 1.0 and 2.3 ± 0.7 ng/ml, respectively, $p < 0.05$; Fig. 1). The mean decrease (Δ) of soluble BAFF was 0.54 ± 1.18 ng/ml and 0.32 ± 2.12 ng/ml in patients with AMR and without rejection, respectively ($p = 0.739$).

Selected Risk Factors in Relation to the Incidence of Combined AMR and ACR

There were no major variations in gender, type of donor, immunosuppression, the number of HLA mismatches, or PRA levels between patients with AMR, simultaneous AMR and ACR, and patients free of rejection (Tables 3, 4). Serum creatinine concentrations were, however, significantly higher

Table 2 Selected risk factors in relation to the incidence of acute antibody-mediated rejection (AMR)

	No rejection		AMR		*p* value
	$n = 17$	Range/(%)	$n = 19$	Range/(%)	
PRA[a]					
<10% ($n = 23$)	11	48%	12	52%	NS[c]
≥10% ($n = 13$)	6	46%	7	54%	
PRA					
<50% ($n = 32$)	15	47%	17	53%	NS
≥50% ($n = 4$)	2	50%	2	50%	
Number of HLA mismatches					
($n = 29$)	4.3 ± 1.6	(0–6)	3.9 ± 1.6	(0–6)	NS
Serum creatinine (μmol/l)[b]					
($n = 36$)	122 ± 22	(82–204)	436 ± 168	(153–980)	<0.0001
BAFF (ng/ml)					
Before transplantation ($n = 36$)	3.5 ± 0.9	(1.8–5.6)	2.9 ± 0.7	(1.9–6.7)	NS
After transplantation ($n = 36$)	3.2 ± 1.0	(1.6–6.6)	2.3 ± 0.7	(1.4–4.2)	<0.05

[a] Panel-reactive antibodies

[b] Time points for serum creatinine measurements were the same as those for performing BAFF measurements

[c] Not significant

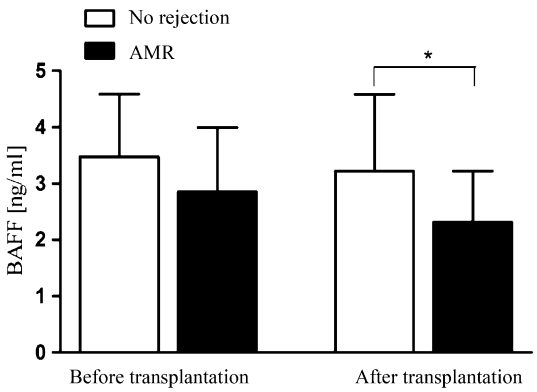

Fig. 1 Concentrations of BAFF before and after transplantation in patients without rejection and patients with AMR (Mann–Whitney test, $*p < 0.05$)

in patients with combined AMR and ACR in comparison with patients without rejection (<0.0001) (Table 4). Before transplantation, BAFF concentrations did not significantly differ between the patient cohorts, although a trend of lower BAFF levels in patients with rejection was observed. In patients with simultaneous ACR and AMR ($n = 9$), however, BAFF levels after transplantation were significantly lower than in patients without rejection ($p < 0.01$) (Table 4; Fig. 2). In patients with AMR only, a trend of lower BAFF was observed compared with patients free of rejection ($p = 0.0653$) (Fig. 2). When comparing the concentrations of BAFF in patients with AMR with the presence of DSA before and after transplantation, seven patients with AMR had DSA before transplantation, while the remaining 12 recipients did not. No correlation was found between BAFF levels and the production of DSA (Fig. 3).

Discussion

As indicated above, the BAFF cytokine is a key regulator of B-cell development, provides signals for maturation to naïve and memory B lymphocytes, and supports the survival of plasmablasts and plasma cells. Concerning its role in organ transplantation, elevated expression of BAFF in peripheral blood cells was observed in patients with abnormal graft function and elevated PRA (Xu et al. 2009). Moreover, patients with high BAFF levels had a higher probability of producing DSA (Thibault-Espitia et al. 2012). High concentrations of BAFF have been also measured in patients before and after immunotherapy using anti-CD52 and anti-CD20 antibodies (Banham et al. 2013; Bloom et al. 2009; Zarkhin et al. 2008). In our study, we compared the concentrations of the soluble BAFF cytokine in patients with and without AMR before and after transplantation with the goal of testing the hypothesis whether the BAFF cytokine can be used as a diagnostic marker of AMR. Our cohorts included a high-risk group of 19 patients who developed AMR; nine of whom also had concurrent ACR. The control group comprised 17 patients without rejection. Analysis of demographic data of the two cohorts did not show a statistically significant influence of gender, age, or

Table 3 Demographic and clinical data of kidney recipients and incidence of concurrent antibody-mediated rejection and acute cellular rejection

	No rejection		AMR[a] + ACR[b]		*p* value
	n = 17	Range/(%)	*n* = 9	Range/(%)	
Recipient age					
n = 26	55 ± 6	(44–66)	53 ± 14	(34–72)	NS[e]
Gender					
Male (*n* = 15)	10	69%	5	31%	NS
Female (*n* = 11)	7	56%	4	44%	
Type of donor					
Living (*n* = 5)	1	20%	4	80%	0.034
Deceased (*n* = 21)	16	79%	5	21%	
Serum creatinine (μmol/l)					
1-month (*n* = 26)	117 ± 32	(81–208)	249 ± 114	(121–426)	<0.01
3-month (*n* = 24)	124 ± 30	(82–204)	209 ± 72	(118–313)	<0.01
6-month (*n* = 23)	113 ± 20	(79–159)	186 ± 76	(101–300)	0.057
12-month (*n* = 25)	104 ± 14	(73–133)	225 ± 104	(107–381)	<0.001
Induction immunosuppression					
No (*n* = 22)	16	80%	6	20%	0.10
Yes (*n* = 4)	1	40%	3	60%	
Maintenance immunosuppression					
FK506[c], MMF[d], Prednisone (*n* = 21)	14	82%	7	78%	NS
FK506, Rapamycin, Prednisone (*n* = 2)	0	0%	2	22%	
Cyclosporine, MMF, Prednisone (*n* = 2)	2	12%	0	0%	
Other (*n* = 1)	1	6%	0	0%	

[a] Antibody-mediated rejection

[b] Acute cellular rejection

[c] Tacrolimus

[d] Mycophenolate mofetil

[e] Not significant

the type of maintenance immunosuppression on the development of AMR. Interestingly, 11 out of the 12 patients, who underwent induction immunosuppressive regimen before transplantation, developed AMR. This finding suggests that these patients were already high risk before transplantation and, in spite of the application of intensive immunosuppressive treatment, they developed acute rejection. Intriguingly, data in the literature concerning the changes in B-cell phenotypes and B-cell subsets after induction immunosuppression with basiliximab are contradictory (Cherukuri et al. 2012; Longshan et al. 2014). The potential effects of basiliximab on BAFF levels/or activity, however, to our best knowledge, have still not been investigated. As far as graft function was concerned, patients with AMR had significantly higher concentrations of serum creatinine at various time points after transplantation in comparison with patients free of rejection. This observation is in line with previously published data, showing that AMR may permanently damage the transplanted organ (Colvin and Smith 2005).

The evaluation of several risk factors of rejection did not show significant effect of the number of HLA mismatches and elevated PRA on the incidence of AMR and ACR. It is well known that high PRA are a risk factor for the development of AMR; however, because of the relatively small number of patients included into our study and probably due to the low sensitivity of the CDC test used for the evaluation of PRA, this relationship could not be demonstrated.

The measured values of the BAFF cytokine before transplantation did not show significant differences between the patient groups with and without rejection. However, a decreasing trend was observed among groups, where patients without rejection showed the highest average values of BAFF compared to the mean values in patients with AMR and simultaneous AMR and ACR. Surprisingly, when determining BAFF levels in the sera of patients obtained after transplantation (at the time of rejection), significantly lower values were found in recipients with AMR (*n* = 19). When analysed separately (patients with AMR only

Table 4 Selected factors in relation to the incidence of acute antibody-mediated rejection and combined antibody-mediated rejection (AMR) and acute cellular rejection (ACR)

	No rejection		AMR		AMR + ACR		*p* value
	$n = 17$	Range/(%)	$n = 10$	Range/(%)	$n = 9$	Range/(%)	
PRA[a]							
<10% ($n = 23$)	11	48%	4	17%	8	35%	NS[c]
≥10% ($n = 13$)	6	46%	6	46%	1	8%	
PRA							
<50% ($n = 32$)	15	47%	8	25%	9	28%	NS
≥50% ($n = 4$)	2	50%	2	50%	0	0%	
HLA mismatches							
$n = 29$	4.3 ± 1,6	(0–6)	3.9 ± 1.6	(0–6)	4.3 ± 1.5	(0–6)	NS
Serum creatinine (μmol/l)[b]							
$n = 36$	122 ± 22	(82–204)	448 ± 178[c]	(153–980)	442 ± 183	(129–736)	<0.0001[d]
BAFF (ng/ml)							
Before transplantation ($n = 36$)	3.5 ± 0,9	(1.8–5.6)	3.0 ± 0.8	(1.9–6.7)	2.7 ± 0.7	(1.7–4.1)	0.07
After transplantation ($n = 36$)	3.3 ± 1.1	(1.6–6.6)	2.7 ± 0.8	(1.4–4.2)	1.9 ± 0.5	(1.0–2.8)	<0.01[d]

[a] Panel-reactive antibodies

[b] Time points for serum creatinine measurements were the same as those for performing BAFF measurements

[c] Non-significant

[d] Compared with the non-rejection cohort

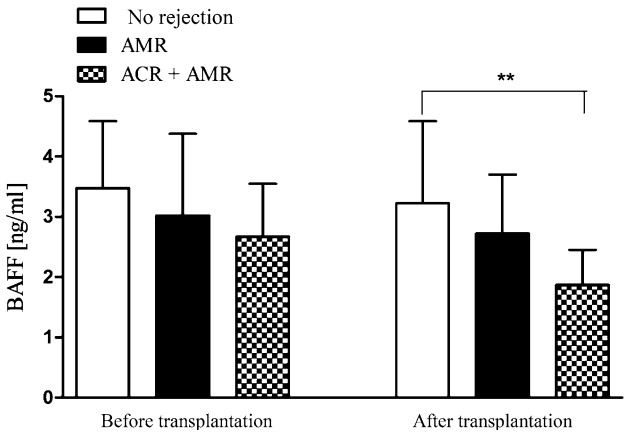

Fig. 2 BAFF levels before and after transplantation in patients free of rejection, with AMR and simultaneous AMR and ACR (Mann–Whitney test $^{**}p < 0.01$)

($n = 10$) and patients with simultaneous AMR and ACR ($n = 9$)), it became evident that the group of patients with AMR had a trend of lower concentrations of BAFF in comparison with the control group ($p = 0.065$). In contrast, patients with simultaneous AMR and ACR had significantly lower concentrations of BAFF vs patients without rejection. When confronted with literature data, as indicated above, Banham et al. (2013) reported increased levels of BAFF in patients with acute AMR who had undergone DSA-incompatible transplantation. In the same study, however, this correlation was not found in HLA antibody-compatible kidney recipients. In other reports, no significant relationship was found between the concentrations of soluble BAFF and the incidence of acute AMR (Snanoudj et al. 2014; Thibault-Espitia et al. 2012; Xu et al. 2009). Interestingly, analysis by flow cytometry found significantly higher levels of membrane-bound BAFF in patients with abnormal renal function (Xu et al. 2009). In our judgement, the lower concentration of BAFF in patients with AMR could be caused by the binding of soluble BAFF by B or plasma cells. The significantly lower levels of BAFF in patients with concurrent AMR and ACR may also be explained by binding of the cytokine on B lymphocytes as well as T lymphocytes, which express membrane receptors for BAFF (BAFF-R, TACI).

In patients with AMR, we also checked the hypothesis whether the production of DSA might correlate with the levels of BAFF before and after transplantation. Of the 19 patients with AMR, seven had DSA before and after transplantation (the remaining 12 patients were DSA negative). We found no statistically significant differences in BAFF levels between the groups with and without DSA. This finding contradicts the data published by Zarkhin et al. (2008), who reported that patients with DSA against HLA class I antigens had higher levels of BAFF. Thibault-Espitia et al. (2012) also observed that renal transplant patients with higher concentrations of BAFF had a significantly greater risk of producing DSA; however, this

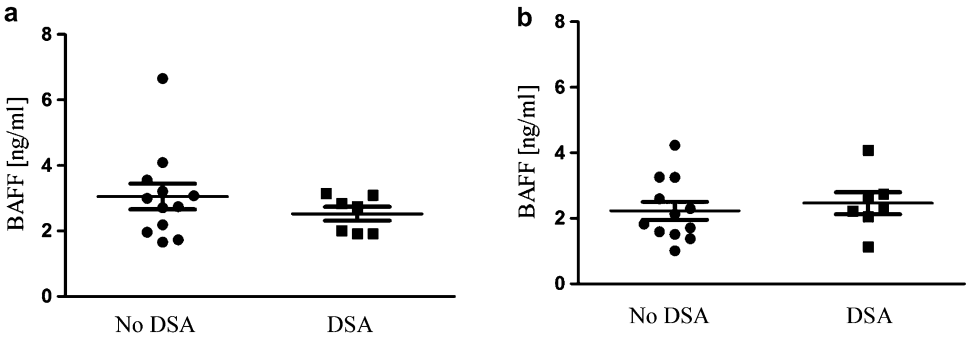

Fig. 3 BAFF concentrations before (**a**) and after transplantation (**b**) and correlation with DSA

finding was not confirmed by another recent study (Snanoudj et al. 2014).

In conclusion, when comparing the concentrations of the BAFF cytokine before transplantation, no significant differences were found between kidney recipients who developed acute AMR and patients free of rejection. The levels of BAFF during AMR were significantly lower in patients with concurrent acute humoral and cellular rejection versus patients free of rejection. Patients who had only acute AMR had a trend of lower concentrations of BAFF. No correlation was found between BAFF levels in patients with AMR and the production of DSA. Our results suggest that soluble BAFF measurements might be helpful as a marker of ongoing AMR and especially of simultaneous antibody-mediated and cellular rejection after kidney transplantation.

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