

Serum BAFF strongly correlates with PsA activity in male patients only – is there a role for sex hormones?

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Abstract

Objectives

To determine the relationship between serum levels of B cell activating factor belonging to the TNF family (BAFF) and disease activity (DAS28) in psoriatic arthritis (PsA) patients.

Methods

Twenty-two male and 31 female psoriasis patients fulfilling the CASPAR criteria for PsA were recruited for the study. Disease activity was recorded using the disease activity score for 28 joints (DAS28). Whole blood and serum samples were analysed for serum BAFF, estradiol, and testosterone levels.

Results

Serum BAFF levels were positively correlated with DAS28 only in male PsA patients ($r=0.669$, $p<0.001$). In male but not female patients, serum testosterone was negatively correlated with DAS28 ($r=-0.632$, $p=0.002$), and serum BAFF ($r=-0.520$, $p=0.018$), respectively. The serum BAFF/ serum testosterone (B/T) ratio showed a strong correlation with DAS28 in male patients ($r=0.743$, $p<0.0001$) and, again, no correlation was found in female participants ($r=0.019$, $p=0.93$). A linear regression analysis showed that the B/T is a good predictor of DAS28 ($r^2=0.586$, $p<0.001$). On the other hand, estradiol levels did neither correlate with PsA activity in male nor female patients in our study population.

Conclusion

Even though a role for B cells in the pathogenesis of PsA has not been established, BAFF levels correlate with disease activity in male PsA patients. Furthermore, serum testosterone in male patients negatively correlates with disease activity and BAFF, respectively. The serum BAFF/serum testosterone ratio might be used as predictor of disease activity in male PsA patients.

Key words

psoriatic arthritis, psoriasis, BAFF/BlyS, testosterone, estradiol, gender difference

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This study was in part sponsored by DFG grant PO 801/3-1.

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Received on January 17, 2010; accepted in revised form on May 18, 2010.

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Abbreviations:

BAFF:	B cell activating factor belonging to TNF family
BCMA:	B cell maturation antigen
BlyS:	B lymphocyte stimulator
BMI:	body mass index
B/T ratio:	serum BAFF/serum testosterone ratio
CRP:	C-reactive protein
DAS28:	disease activity score (28 joints)
DHEA:	dihydroepiandrosterone
ELISA:	enzyme-linked immunosorbent assay
ESR:	erythrocyte sedimentation rate
FSH:	follicle stimulating hormone
LH:	luteinising hormone
PsA:	psoriatic arthritis
RA:	rheumatoid arthritis
SLE:	systemic lupus erythematosus
TACI:	transmembrane activator and calcium modulator and cyclophilin ligand interactor
WBC:	white blood cell count

Introduction

PsA is distinct from rheumatoid arthritis (RA) by different clinical presentations and different immunological features. Inflamed PsA synovial tissue contains relatively more T cells and fewer macrophages as compared to RA (1). With respect to B cells, the significance of those cells is increasingly recognised in the pathogenesis of arthritis (2, 3). As a histopathological indicator of B cell involvement, germinal centre-like structures have been described in synovial tissues of RA but also PsA patients (4-6). The prevalence of highly organised germinal centre-like structures in a high percentage of patients with PsA and regression of these germinal centre-like structures following effective therapy points to an involvement of B cells in the pathogenesis of PsA (4). Further evidence of B cell involvement in RA and PsA is derived from the positive response observed in patients treated with B cell targeting therapies. While it is generally accepted that the anti-CD20 treatment is beneficial in RF-positive RA patients, results in patients with RF-negative RA are not similarly convincing (7, 8). In PsA, there is no known involvement of autoantibodies in the disease process, and case reports, where anti-CD20 was used to treat RA and SLE in patients suffering from concomitant psoriasis, reported a deterioration of skin lesions during treatment. However, the effect on psoriatic arthritis might be different and was not determined in this study (9).

A novel B-cell targeting therapy is the inhibition of the B cell activating factor (BAFF), which belongs to the tumour necrosis factor family (10). BAFF, also known as B lymphocyte stimulator (BlyS), promotes proliferation and survival of some autoreactive B cells (10, 11). BAFF is produced by cells of the myeloid lineage such as macrophages, monocytes and dendritic cells, and the expression can be induced by cytokines like INF- γ and IL-10 (12). BAFF interacts with three known receptors expressed on B cells: B cell maturation antigen (BCMA), transmembrane activator and CAML interactor (TACI) (13), and BAFF receptor (14). Strong evidence from animal models and clinical studies

suggests an important role of BAFF in some autoimmune disorders like systemic lupus erythematosus (SLE), Sjögren's syndrome, and RA (13, 15-17). Initial clinical trials show a beneficial effect of BAFF-inhibiting therapies in RA and SLE patients (18, 19). However, the role of BAFF in patients with PsA is not yet known. Therefore, the objective of the present study was to determine the relationship between serum BAFF levels and disease activity in patients with PsA.

Patients and methods

Subjects

From May 2008 until October 2008, 56 patients were recruited from our outpatient clinic at the University Medical Centre of Regensburg and classified according to the CASPAR criteria (20). All participants fulfilled the CASPAR criteria for PsA. Patients that additionally suffered from osteoarthritis (n=4) were excluded from analysis because it is not possible to clearly distinguish between PsA disease activity and osteoarthritis disease activity. The ethics committee of the University Regensburg approved the study (no. 04/165), and informed consent was obtained from all study participants.

Gender, age, medication, body mass index (BMI), menopausal status, duration of PsA, total tender and swollen joints, disease activity score (DAS28) (21, 22), and psoriasis area severity index (PASI) (23) were recorded (Table I). DAS28 and PASI scores were determined by the same investigator throughout the study. There was no significant difference between female and male patients regarding all parameters, except ESR, which was significantly higher in female as compared to male patients. There was a trend towards increased use of anti-TNF in the male study population.

Laboratory testing

Venous blood was collected between 8 am and 10 am. Serum aliquots were immediately stored at -80°C until analysis. BAFF was assayed by commercially available antigen-capture enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis,

Competing interests: none declared.

USA). On the day of blood collection, testosterone, estradiol, luteinising hormone (LH), follicle stimulating hormone (FSH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and number of white blood cells (WBC) were determined by standardised procedures utilising commercially available assays.

Statistical analysis

All analyses and data presentation were performed using Sigma Stat and Sigma Plot software (SPSS, Chicago, IL). Female participants with pre-ovulatory estradiol serum levels (>120 pg/ml, $n=3$) were excluded from analysis and testosterone levels were not available for 6 female participants. Serum BAFF levels were not normally distributed, and therefore non-parametric tests were used for analysis. Correlations were determined by Spearman rank correlation analysis. Differences of medians between two different groups were determined using the Mann-Whitney test. One-sided tests were performed in partial correlations. To analyse proportional differences between the genders (*e.g.* use of medication) the Z-test was performed. A p -value ≤ 0.05 was considered significant.

Results

BAFF levels correlate with DAS28 in male but not in female PsA patients

As a measure of disease activity, DAS28 was determined in all PsA-patients according to standard protocols. DAS28 has been shown to discriminate between treatment and placebo in patients with PsA (24). However, DAS28 was criticised as a measure of disease activity, because feet and distal interphalangeal joints are excluded from analysis, which might lead to an underestimation of disease activity in PsA. Therefore, we also determined the total number of swollen and tender joints in our patients, which both showed a strong positive correlation with DAS28 ($r=0.427$; $r=0.719$; $p<0.001$). Analysis was also performed using DAS44 instead of DAS28. However, the conclusion of the data remained the same. In the combined analysis of female and male PsA patients, BAFF levels

Table I. Patient characteristics.

	Male (SD)	Female (SD)	Total (SD)
n	21	31	53
Sex (%)	41.5	58.5	100
Age (yrs)	44.5 (9.2)	46.7 (15.4)	45.8 (13.2)
BMI (kg/m ²)	28.2 (5.2)	26.8 (5.7)	27.4 (5.6)
DAS28	2.5 (1.59)	3.0 (1.1)	2.8 (1.3)
tender joints	7.7 (14.6)	8.5 (11.4)	8.1 (12.8)
swollen joints	3.6 (11.6)	1.7 (3.5)	2.5 (7.9)
Duration PsA (yrs)	8.2 (7.4)	10.7 (11.8)	9.7 (10.3)
PASI score	4.2 (4.2)	3.9 (4.1)	4.0 (4.1)
affected skin (%)	7.6 (12.3)	6.0 (8.5)	6.7 (10.3)
axial involvement (%)	47.6	32.3	38.5
Dactylitis (%)	4.8	9.7	7.7
Enthesitis (%)	28.6	48.4	40.4
CRP (mg/l)	6.2 (9.6)	8.2 (11.8)	7.3 (10.9)
ESR (1h)*	10 (6)	18 (11)	14 (10)
WBCs (1/nl)	8.1 (2.0)	8.2 (2.5)	8.2 (2.3)
Prednisolone (%)	9.1	12.9	11.3
MTX (%)	40.9	32.3	35.8
anti-TNF (%)	31.8	12.9	20.8
other DMARD (%) ¹	0.0	3.2	1.9
NSAID (%)	45.5	45.2	45.3

BMI: body mass index; CRP: C-reactive protein; DAS28: disease activity score (28 joints); DMARD: disease modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; n: number of patients; MTX: methotrexate; NSAID: non steroidal anti inflammatory drugs; PASI: psoriasis area severity index; SD: standard deviation; WBC: white blood cells; yrs: years.

¹other DMARDs used: leflunomide, sulfasalazine, cyclosporine A.

*Significant difference between female and male patients, Mann-Whitney test: $p=0.006$.

tended to correlate positively with DAS28 ($r=0.273$, $p=0.052$). However, a subgroup analysis revealed a difference between male and female patients concerning the correlation with DAS28 (Fig. 1A, B). While there was no difference in absolute BAFF serum levels between women and men (male: 852 pg/ml ± 209 ; female: 1010 pg/ml ± 313 ; *n.s.*), there was a highly significant positive correlation between BAFF levels and DAS28 in male patients but not in female PsA patients (Fig. 1A, B). Analysis of the relationship between tender joints, including feet and distal interphalangeal joints, and serum BAFF showed the same gender difference (male: $r=0.440$, $p=0.045$; female: $r=0.073$, $p=0.7$).

To exclude a potential difference in pre- and post-menopausal female patients with respect to a relationship between serum BAFF concentrations and DAS28, further subgroup analyses were performed. A significant relationship between DAS28 and BAFF serum levels could not be detected in post- or pre-menopausal female PsA

patients ($r=0.269$, $r=0.326$; *n.s.*), indicating a difference independent of the female hormonal status. There was a trend towards longer duration of PsA in female patients, however neither female nor male PsA duration correlated with BAFF serum levels ($r=-0.251$; $r=0.012$; *n.s.*).

Another potential bias in the data was the different use of anti-TNF between male and female patients (Table I). Although the proportional difference (anti-TNF: male: 31.8% vs. female: 12.9%) was not statistically significant (Z-test: $p=0.184$), we excluded patients treated with anti-TNF from analysis. However, the conclusion of the data, in particular the gender difference in the correlation of serum BAFF and DAS28 remained (male: $r=0.600$, $p=0.017$; female: $r=-0.103$, $p=0.613$), arguing against a bias due to the use of anti-TNF.

Additionally, we analysed the data only including patients with axial involvement, even though the proportional difference (axial involvement: male: 47.6% vs. female: 32.3%) was not statistically significant (Z-test: $p=0.184$).

Including only patients with axial involvement, increased the correlation between DAS28 and serum BAFF in male patients ($r=0.905$, $p<0.001$), but decreased the correlative relationship between DAS28 and serum BAFF in female participants ($r=0.042$, $p=0.892$), arguing for a gender difference even within the subgroup of patients with axial involvement.

A recent report showed that B cell depleting therapy with anti-CD20 resulted in worsening of skin psoriasis (9). However, a correlative relationship between PASI or area of skin involvement, respectively, and serum BAFF levels was not detected in male or female study participants.

DAS28 is negatively correlated with testosterone levels in male PsA patients.

The striking sex difference depicted in Figure 1 prompted us to further investigate the potential factors underlying this observation. We therefore determined hormone levels of LH (female: 24.3 ± 22.4 IU/l; male: 3.7 ± 1.4 IU/l; $p=0.008$), and FSH (female: 39.9 ± 37.3 ; male: 4.6 ± 2.6 IU/l; $p=0.004$), which were significantly different between female and male participants. Furthermore, testosterone serum levels were markedly lower in female versus male participants (Fig. 2A). Estradiol serum levels were not significantly different between male (male: 30.4 ± 16.4 pg/ml; female: 37.6 ± 43.2 pg/ml; $p=0.58$) and female participants. We then analysed the correlation of LH, FSH, estradiol and testosterone with disease activity (Fig. 2B, C and data not shown). For levels of LH, FSH, and estradiol including subgroup analysis of pre- and postmenopausal status, no correlation was found with DAS28 (data not shown). However, in male (Fig. 2B) in contrast to female patients (Fig. 2C), DAS28 was negatively correlated with serum testosterone pointing towards a possible anti-inflammatory role of testosterone in PsA.

BAFF is negatively correlated with testosterone levels in male patients

Due to the correlation of BAFF but also testosterone levels with DAS28, respectively, the possibility arises that sex hormones might influence arthritis

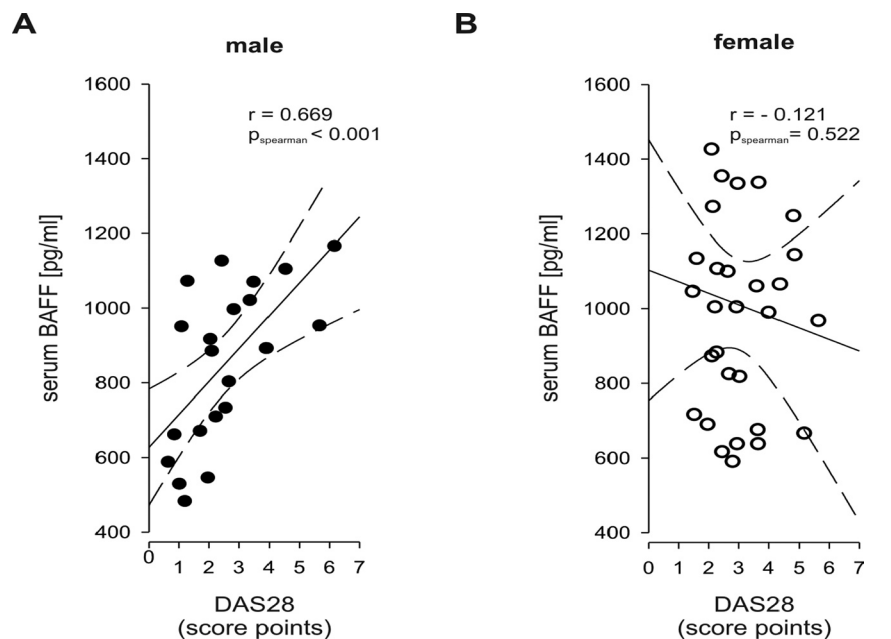


Fig. 1. Correlation between BAFF serum levels and DAS28 in PsA patients. (A) only male patients; (B) only female patients. Dashed lines represent the 95%-confidence intervals of the linear regression line.

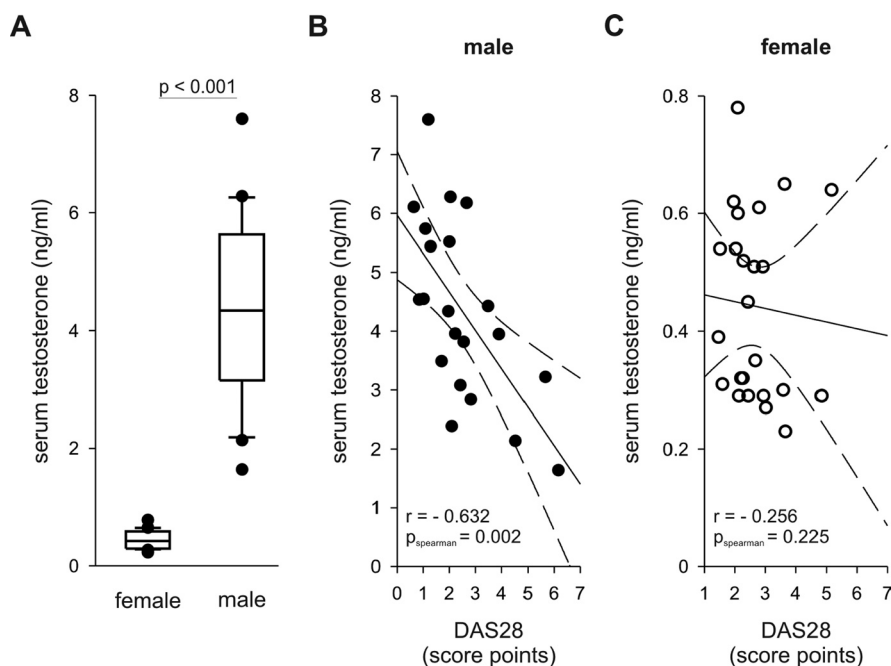


Fig. 2. Differences in female and male PsA patients – testosterone levels and correlation with DAS28. (A) Testosterone serum levels in female and male patients. (B and C) Correlation of testosterone serum levels and DAS28 in male (B) and female (C) participants. Dashed lines represent the 95%-confidence interval of the linear regression line.

activity by regulating BAFF serum levels. We therefore analysed the relationship between serum levels of BAFF, testosterone, LH, FSH, and estradiol. Serum concentrations of BAFF and testosterone in male patients showed a significant negative correlation (Fig. 3A), whereas serum levels of BAFF and

estradiol were positively correlated in male patients (Fig. 3C). However, serum estradiol was negatively correlated with BAFF in female patients as opposed to male patients (Fig. 3C, D). Serum levels of LH, FSH, in male and testosterone, LH and FSH in female patients did not reveal any correlation with BAFF

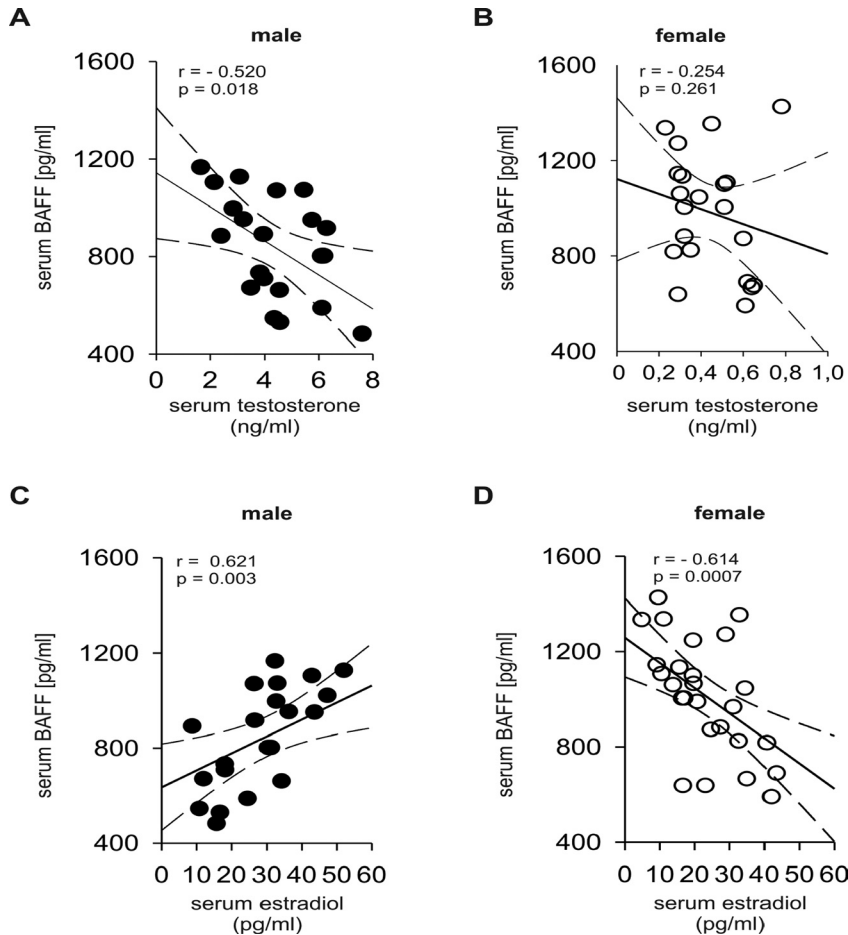


Fig. 3. Correlation of serum testosterone (A, B) and serum estradiol (C, D) with serum BAFF. (A, C) male patients; (B, D) female patients. Dashed lines represent the 95%-confidence interval of the linear regression line.

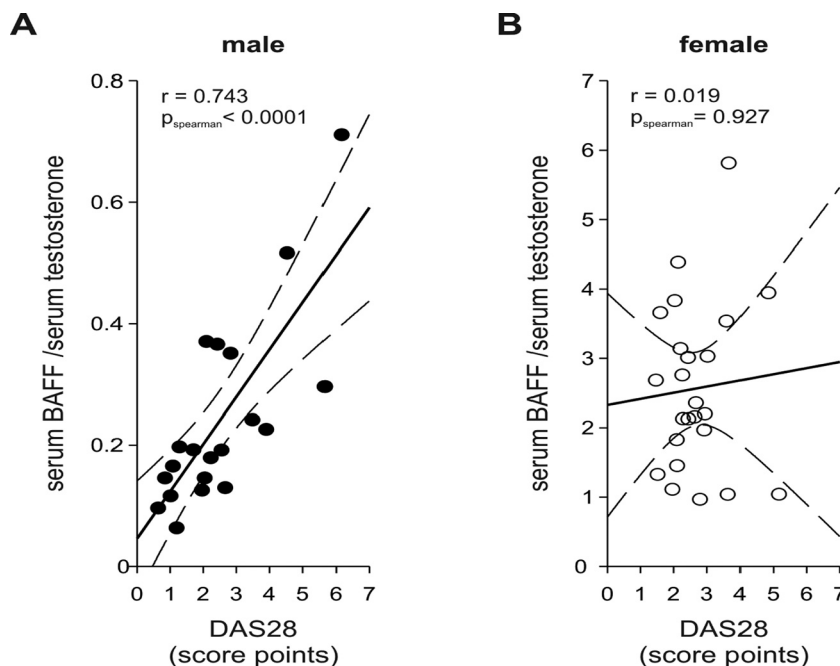


Fig. 4. Correlation of the serum BAFF/ serum testosterone ratio with DAS28 in (A) male and (B) female patients. Dashed lines represent the 95%-confidence interval of the linear regression line.

levels (Fig. 3B and data not shown). These results indicate that a correlation of serum BAFF levels with testosterone is only observed when testosterone serum levels are in the high range, as observed in male PsA patients. With respect to the relationship between serum estradiol and serum BAFF there might be opposing mechanisms between male and female PsA patients.

Serum BAFF and serum testosterone both show partly independent correlation with DAS28

Up to this point, our results indicate that activity of PsA might be related to testosterone levels in male patients by possibly regulating BAFF expression. To test the hypothesis that the correlation of serum BAFF levels and DAS28 might be independent of testosterone concentrations, we performed a partial correlation analysis. Results demonstrate that serum BAFF levels correlate with DAS28 in male patients even after controlling for serum testosterone levels ($r=0.445$; $p=0.028$). A correlation was again not observed in female PsA patients ($r=-0.180$; $p=0.206$). However, the correlation of serum BAFF levels and DAS28 was weakened when compared to results obtained without controlling for serum testosterone, thus showing that the relationship is not completely independent of testosterone levels. The same was found in the opposite case when controlling for serum BAFF and analysing the correlation between serum testosterone and DAS28 (male: -0.479 , $p=0.038$; female: -0.075 , $p=0.735$). Taken together, these results support the hypothesis that serum levels of BAFF and testosterone are in part interdependent concerning the correlation with PsA activity.

To create a combined possible predictive parameter for DAS28 in male PsA patients, we generated a new variable by calculating the serum BAFF/serum testosterone (B/T) ratio for each patient and analysed its relationship with DAS28. We found a highly significant positive correlation between the B/T ratio and DAS28 in male patients (Fig. 4A) but again not in female patients (Fig. 4B). The correlation of the ratio with DAS28 was stronger than the correlation of se-

rum BAFF and DAS28 in male patients. To test if the combined parameter could serve as predictive variable for DAS28 we performed linear regression analysis and found that the B/T ratio can explain over 56% of the DAS28 value in male PsA patients ($\text{DAS28}_m = 0.694 + (0.00752 \cdot \text{BAFF/Testosterone}_m)$, adjusted $r^2=0.563$, $p<0.001$). These results indicate that the B/T ratio might be used as predictive parameter in male PsA patients. We analysed an equivalent serum BAFF/ serum estradiol ratio in female patients, however, again, we did not detect any significant correlation with DAS28 in female PsA patients.

Discussion

BAFF-targeted therapy is a new approach to modulate "B-cell dependent" rheumatic diseases like RA and SLE (25). Since autoantibodies do not play a known role in PsA, the regulation of B cell function has not been within the focus of PsA research for several years. However, the present data indicate a possible link between BAFF and the activity of PsA.

Our data show a striking gender difference with regard to serum BAFF levels, demonstrating a close correlation with disease activity in male patients only. Gender differences in autoimmunity are well-recognised, *e.g.* the incidence rates of many autoimmune disorders like multiple sclerosis, systemic sclerosis, RA, SLE, and many more show a clear female to male preponderance (26, 27). For PsA, it was generally accepted that there are no significant gender differences. Studies demonstrating an earlier onset of symptoms in female patients as compared to male patients are conflicting (reviewed in ref. 28). However, epidemiologic data collected before the publication of the CASPAR criteria in 2006 (20) have to be interpreted with caution because an earlier classification of PsA was based on unevaluated diagnostic criteria. However, our data strongly support the hypothesis that a gender difference exists in PsA, at least, with respect to B cell involvement and influence of sex hormones in the disease process.

Due to the striking gender difference, we investigated the relationship between

levels of serum BAFF and sex hormones. The data indicate a possible opposite involvement of testosterone and estradiol in BAFF regulation in male participants. In female participants only estradiol showed a negative correlation with serum BAFF, whereas testosterone levels in females might be too low to allow effects on BAFF serum levels. A possible influence of sex hormones on the production of BAFF has not been documented in the literature yet. However, a concentration-dependent inhibition of BAFF production by another steroid hormone, dexamethasone, was recently demonstrated in synovial-like fibroblasts of RA patients (29), which supports the concept that BAFF expression might be regulated by steroid hormones.

There are only a few studies that determine sex hormones in PsA. The first study to demonstrate the course of HPA axis-related hormones in patients with PsA showed that an increase of serum cortisol relative to sex hormones, like androstenedione and 17-hydroxyprogesterone, was accompanied by clinical improvement of PsA following anti-TNF treatment with etanercept (30). A clear anti-inflammatory effect of testosterone or its precursor dehydroepiandrosterone (DHEA), and a proinflammatory role of some oestrogens is known in many autoimmune diseases, such as RA (27, 31). However, one study in 67 psoriasis patients demonstrated an increase in DHEA serum levels following haemodialysis, which correlated with an improvement in skin psoriasis (32), indirectly indicating an anti-inflammatory potential of androgens in psoriasis, which is also suggested by our data, showing a negative correlation of serum testosterone and DAS28 in male PsA patients. To explain the gender difference, one may speculate that testosterone levels need to reach a certain threshold to exert an anti-inflammatory potential.

From other studies it is clear that the function of the gonadal axis and therefore serum testosterone is usually suppressed by pro-inflammatory cytokines (33). Thus, testosterone levels are low in patients with high systemic inflammation and improve after adequate therapy (34). In our study cohort, overall

inflammation was only moderate. Thus, we did not observe a relevant suppression of testosterone or estradiol in male or female patients that still showed levels within the physiological range.

Other differences between male and female participants that might possibly lead to different results, such as smoking habit, alcohol use, or differences in NSAID therapy, were not observed (Table I and data not shown). There was a trend towards higher inflammatory activity in PsA women, which might be due to lower serum testosterone levels in female participants. However, those minor differences cannot explain the striking and highly significant differences in correlation analyses of female and male patients.

With respect to skin psoriasis, one study shows a positive correlation between the PASI score and serum BAFF levels, possibly indicating a negative role for B cells (35). In contrast to the latter study, we could not detect a correlation of PASI and serum BAFF in our study population. This might be due to the low grade of skin involvement in our patients ($\text{PASI } 4.0 \pm 4.1$). In addition, all of our participants fulfilled the CASPAR criteria for PsA, whereas only 9.8% of the patients in the above-mentioned study also suffered from PsA. These results suggest that BAFF might play different roles in skin psoriasis vs. PsA.

A limitation of our study is the relatively small sample size. Especially in subgroup analyses within female and male participants (*e.g.* analysis of patients with axial involvement only) data have to be interpreted with caution. However, even with small sample sizes the calculated correlation coefficients are highly significant, which strengthens the relevance of our observations. Another limitation might be the low overall inflammatory activity in our study population (Table I). It is possible that, if inflammatory activity increases, the differences between male and female patients would even out. This is a hypothesis that needs to be tested in additional studies. An additional limitation of our study is the correlative nature of our findings. However, our findings generate hypotheses that could be

tested in further experiments, *e.g.* that there exists an intrinsic gender difference in the pathogenesis of female and male PsA, which might suggest different treatment approaches for female and male patients, respectively.

In conclusion, our study shows that, even though a role for B cells in the pathogenesis of PsA has not been established yet, BAFF levels correlate with disease activity in male PsA patients only. This gender difference is in part explained by high serum testosterone in male patients, which negatively correlates with disease activity and BAFF, respectively. We further revealed a possible influence of the sex hormones testosterone and estradiol on serum BAFF levels, which also differs between genders (Fig. 3). Finally, we showed that the serum BAFF/serum testosterone ratio might be used as predictor of disease activity in male PsA patients.

Acknowledgements

We want to thank Madlen Melzer for the excellent technical assistance.

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