Psychiatria Danubina, 2013; Vol. 25, No. 3, pp 227-235 *Original paper*

CHILDHOOD MALTREATMENT AND ADULT PROINFLAMMATORY STATUS IN PATIENTS WITH MAJOR DEPRESSION

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received: 1.3.2013; revised: 18.6.2013; accepted: 2.8.2013

SUMMARY

Background: *An increasing body of research considers the immunological effects of major depression. It remains an open question, whether depression itself acts in an immunomodulatory fashion or whether other factors related to depression result in these immunological effects. Regardless, major depression is often the result of early life stress, the implications of which are not satisfactorily understood.*

Subjects and methods: *Early life stress was retrospectively evaluated in 25 depressed inpatients via the CTQ (Childhood Trauma Questionnaire). Its impact on immunological biomarkers (fibrinogen, SAA, CRP, adiponectin, TNF-α, resistin, and sE-selectin) in adulthood was assessed via multiple regression analyses. Parental bonding was assessed via the PBI (Parental bonding questionnaire), severity of depression with the HDRS-17 (Hamilton-Depression-Rating Scale).*

Results: *Nearly all patients had experienced a parental style of affectionless control. Physical neglect significantly predicted fibrinogen levels (R^2=0.42, adjusted R^2=0.27, β=0.56, p=0.04). Severity of depression was not associated with immune markers.*

Conclusion: *Childhood maltreatment was linked to fibrinogen levels in our sample. Thus, inflammation may be an important mechanism mediating the adverse effects of early life stress on adult health in patients with major depression.*

Key words: *childhood maltreatment - major depression - subclinical inflammation*

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INTRODUCTION

Various studies have demonstrated an association between major depression and immuno-activation in the form of mild inflammatory responses, possibly initiated by cytokines (Frodl et al. 2012, Maes et al. 1990, Kim et al. 2007, Sperner-Unterweger 2005, Zeugmann et al. 2010, Zeugmann et al. 2012), thereby putting patients at risk for serious comorbidities such as cardiovascular diseases with all their implications. What remains unclear, is, whether depression itself causes the immuno-response, or whether there are other variables associated with depression or with the immune system that are the actual triggering force.

It has been suggested elsewhere, that depression and cardiovascular disease might share one common underlying factor, i.e. that they are two possible outcomes that result from the same prior stress-related insult to the body (Miller & Blackwell 2006, Mosovich et al. 2008). More specifically, pro-inflammatory cytokines, released in response to stress, may reduce serotonin levels and subsequent platelet aggregation causing both depression and atherosclerosis.

The pathways for an intact immune system as well as a healthy mind are established early on in life and both develop in dialogue with environmental experiences. Given that the consequences of early adverse experiences can perpetuate into adulthood, it is important to investigate whether childhood maltreatment also affects the immunocompetence of patients with depression.

A history of childhood stress such as experiencing the world to be insecure, perceiving oneself as being unlovable or not valuable and regarding the future as not being trustworthy caused by emotional abuse and neglect, sexual and physical abuse as well as physical neglect all increase the risk of developing a depressive disorder in adulthood (Rojo-Moreno et al. 1999, Ritchie et al. 2009, Wright et al. 2009, Subic-Wrana et al. 2010).

The immunological sequelae of early adverse events have been investigated in animal studies, both in terms of their short-lived and prolonged effects. Reite and colleagues were the first group to demonstrate a disturbance in the immune system subsequent to the disruption of a peer-attachment bond in pigtailed monkey infants (Reite et al. 1981). Subsequent reports showed a suppressed immune response in infant bonnet macaques associated with maternal separation (Laudenslager 1982) and passive behaviours identical to behaviours triggered by the activation of the acute phase response (Hennessy et al 2004, Hennessy et al. 2010) during isolation of guinea pig pups.

Long term consequences of early life stress on the immune system were first considered by Laudenslager et al., who showed that monkeys with early separation experiences had lower proliferation responses to B and T cell mitogens as adults (Laudenslager 1985). Moreover, repeated separation from their dams can lead to enhanced cytokine response during influenza viral infection in adulthood in mice (Avitsur et al. 2006).

As far as human studies are concerned, severe stress in the form of bereavement has been found to produce

an abnormality in immune function in the following weeks and months (Bartrop 1977, Buckley et al. 2012, Schleifer et al. 1983). Short term laboratory marital interaction studies have demonstrated that negative and hostile behaviours during marital disagreements promote immune dysregulation (Kiecolt-Glaser et al. 2005). In an investigation of married couples that could be interpreted in terms of long-term consequences of rearing conditions, Gouin et al. found that individuals with higher levels of attachment avoidance had larger interleukin-6 (IL-6) responses to a marital disagreement compared to less avoidant individuals (Gouin et al. 2009). Attachment avoidance is a behaviour expressed in relationships that has been learned early on in life, mirroring that the persons considered have experienced attachment to be unsafe, unstable or unpredictable when they grew up. Thus the study indirectly showed that unfavourable rearing conditions can have an impact later on in life in stressful situations also on a physiological level.

In a more direct investigation of adverse childhood experiences and their role in acutely stressful situations in adulthood, Carpenter et al. and Gouin et al. report enhanced IL-6 responses to a stress task or daily stressors, respectively, in adults with a history of childhood abuse (Carpenter et al. 2010, Gouin et al. 2012). Similarly, Pace et al. provided evidence for an exaggerated inflammatory response to stress in depressed male patients with a history of early life stress during a stress challenge (Pace et al. 2006). However, early life stress was not associated with immune variables as such, but only with Hamilton Depression Rating Scale scores in this study.

Contrasting this, and shifting the focus away from acutely stressful situations, Danese et al. demonstrated that childhood maltreatment led to elevated pro-inflammatory markers at age 32 (Danese et al. 2007). In a different set of analyses from the aforementioned study, Danese et al. argued that the effects of childhood maltreatment significantly attenuated the association between depression and high levels of hsCRP in depressed 32-year olds in comparison to controls - thereby providing the first pieces of evidence for the hypothesis that depression itself is not the cause of immunoactivation in depressed patients, but possibly early life stress (Danese et al. 2008).

With the current study we aim to comprehensively assess the effects of adverse childhood experiences on numerous different proinflammatory markers in adult inpatients with major depression.

SUBJECTS AND METHODS

Subjects and study design

Subjects are members of the ”Endophänotypisierung affektiver Erkrankungen” (“endophenotyping of affective disorders”) study, part of which is presented here. 58 of the original study members (n=71) are included in the current study. Patients were recruited when referred to the Clinic for Psychiatry and Psychotherapy at the University Hospital Berlin – Charité, Campus Benjamin Franklin between 2005 - 2007. The study was approved by the ethics committee of the Charité and all patients gave their written informed consent to participate. All patients suffered from a depressive episode when admitted to the hospital; the individual diagnosis varied within the range of the affective disorders spectrum (F31, F32, F33 for ICD-10 diagnoses and 296.XX for DSM-IV diagnoses, respectively).

Patients with acute respiratory infections within the last two weeks before assessment or during the study, any active medical illnesses that could etiologically be related to the ongoing depression, immune and autoimmune diseases, anti-inflammatory medication, a history of drug or alcohol abuse within 1 year prior to admission, a schizophrenic or schizoaffective disorder were excluded from the study.

Data was assessed at two time points: at T1 within a few days after referral to the clinic and at T2, which was 4-5 weeks after the beginning of inpatient treatment. Sociodemographic variables were collected at T1.

Questionnaires concerning the assessment of early life stress and parental bonding were sent to the patients after they had been released from the clinic in order to avoid a negative bias when answering the questions due to severe depression (Murphy et al. 2010). Of the 58 patients that were initially approached, 25 returned all questionnaires and these were used for further analysis. Despite the comparatively low number of subjects, all patients were thoroughly investigated and the data set is complete. Statistical analyses were kept simple so that we could attain useful and meaningful results despite the small number of subjects. The results will be useful in the sense of “signal detection” in further studies.

Clinical and laboratory data were anonymous, and all ratings and interviews were performed either by a trained psychiatrist or clinical psychologist who was blind to the immunological results.

Early life stress

Early life stress experiences were quantified using the German version of the Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 1994, Wulff 2007) which retrospectively assesses early traumatic stress during childhood and adolescence, examining five forms of maltreatment – emotional, physical and sexual abuse, and emotional and physical neglect as well as minimization/denial.

Parental bonding

Parental bonding was assessed using a German version of the Parental Bonding Instrument (PBI) (Lutz et al. 1995) which retrospectively evaluates parental bonding for each parent during to the first 16 years of life. Two scales termed “care” (depicting the dimension of care vs. indifference/rejection) and “overprotection”

(depicting the dimension of overprotection vs. allowance of autonomy and independence) operationalise parental styles from the child's perspective. The "care" and "overprotection" scores can be assigned to one of four quadrants:

- affectionate constraint (high care, low protection);
- affectionless control (high protection, low care);
- optimal parenting (high care, high protection);
- neglectful parenting (low care, low protection).

Adult inflammation

Antecubital venipunctures following an overnight fast took place in the early morning hours (always between 8:00 and 9:00 a.m.). The blood was then centrifuged at 3000g for ten minutes, immediately divided into aliquots, and frozen at –70°until analysis.

Inflammatory parameters were analyzed using standard ELISA for adiponectin, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), resistin, soluble E-selectin (sE-selectin), and CD40ligand (CD40L) (all R&D Systems). Serum-amyloid A (SAA), C-reactive protein (CRP), and fibrinogen were analyzed as described earlier (Koenig 1999).

Due to technical difficulties in the laboratory assessing the inflammatory biomarkers, levels of IL-6 were only available for 13 and CDL40 only for 12 subjects. All markers with less than 20 samples were excluded from further analysis.

Major Depression

Severity of depression was quantified with the HDRS (Hamilton-Depression Rating Scale, 17-item version) (Hamilton 1969). Additionally, we also assessed the lifetime number of depressive episodes, duration of the current episode and suicidal attempts in the past.

Statistical analysis

All variables were tested for normality of distribution by means of Kolmogorov-Smirnoff tests. A drop-out analysis was conducted to test for differences between those patients that returned the questionnaires and those who did not. For this purpose, independent samples *t*-tests were carried out. Mann Whitney U-tests were used to assess group differences in variables that were not normally distributed. Chi-square tests were applied to dichotomous variables. Correlations between the immune markers at the two time points were carried out and average scores computed for further analysis. To estimate the relative contribution of early life stress as measured by the CTQ and other potentially contributing variables (HDRS scores, age, sex) on immunological measures, we performed a multiple hierarchical regression analysis. Demographic variables were entered into the first step, CTQ treatment domain (i.e. emotional neglect, physical neglect, emotional abuse) in the second step, and severity of depression (HDRS scores) were added in a third step. All statistical analyses were performed using the PASW software, version 18.0 for Macintosh.

RESULTS

Drop out analysis

Patients who returned their questionnaires did not differ on any of the immunological, clinical or demographic measures from the group that did not return the questionnaires concerning early life stress and parental bonding.

Socio-demographic and clinical characteristics of the current sample

The demographic and clinical characteristics of the study sample are summarized in Table 1 below.

Table 1. Socio-demographic and clinical variables

Variable		
Age (years)	47.80	(15.02)
Sex (male/female) (n)	8/17	
Episode (n)	4.00	(3.35)
Length of episode (weeks)	33.96	(55.79)
Suicide attempts in the past (n)	0.43	(0.84)
HDRS-score T1	21.64	(6.59)
HDRS-score T2	13.11	(4.81)

Values are depicted as means (± standard deviation), unless otherwise stated

Parental bonding

Seven patients did not complete a questionnaire regarding their father, as they had been raised by their mothers alone. Nearly all patients rated the parental styles of their parents as "affectionless control", both for their mothers and fathers as shown in Table 2.

Table 2. Parental bonding assessed with the PBI

Maternal parental style	n
affectionate constraint	1
affectionless control	18
optimal parenting	4
neglectful parenting	2
Paternal parenting style	
affectionate constraint	1
affectionless control	12
optimal parenting	1
neglectful parenting	4

Childhood trauma

Table 3 shows a summary of patients' scores on the CTQ's different subscales. Highest scores were obtainned on the two subscales considering emotional maltreatment. False negative trauma reports are negligible as depicted by the minimization/denial scale.

Table 3. Means ±standard deviations (SD) of CTQ-subscales

CTQ- subscale	mean	±SD
Emotional abuse	11.86	5.35
Physical abuse	7.46	3.24
Sexual abuse	6.50	4.18
Emotional neglect	14.92	5.60
Physical neglect	9.52	2.90
Minimization/denial	0.40	0.71

Grouping the patients according to severity of early adverse events across subscales of the CTQ revealed that most patients of our sample had experienced early stress in the form of neglect and emotional cruelty. Sexual and physical abuse were not very common (Table 4).

Immune markers

Immune markers' measures were correlated at the two time points assessed and an average score for each immune marker was calculated for further analyses (Table 5).

Table 5. Pearson's correlations of the immunological markers at T1 and T2

Marker	Pearson's correlation r
Fibrinogen	0.42*
SAA	0.65**
CRP	0.64**
Adiponectin	0.44*
TNF-α	0.46*
Resistin	0.33
sE selectin	0.62*

$p<0.05$, ** $p<0.001$

Multiple Regression Analyses

The first model of the regression analysis assessing the influence of age and sex on fibrinogen did not reach significance ($F_{2,22}=8.23$, $p=0.45$). The second model with the CTQ subscales included, significantly predicted (in the form of physical neglect) fibrinogen scores ($F_{5,19}=2.80$, $p=0.05$). When severity of depression was added to the third model (HDRS scores at T1 and T2) it did not prove to be significant ($F_{7,17}=1.81$, $p=0.15$) (Table 6).

Table 4. Severity of early adverse events across different subscales of the CTQ

Scale	None-minimal (n)	Low-moderate (n)	Moderate-severe (n)	Severe-extreme (n)
Emotional abuse	8	7	2	8
Physical abuse	17	3	3	2
Sexual abuse	19	2	3	1
Emotional neglect	3	10	4	8
Physical neglect	7	6	6	6

Table 6. Results of the multiple regression analysis for fibrinogen

	B	SE B	ß	p	R^2	adjusted R^2
Step 1					0.07	-0.02
constant	3.51	0.74		0.00		
age	0.00	0.01	0.01	0.95		
sex	-0.04	0.31	-0.26	0.22		
Step 2					0.42	0.27
constant	2.33	0.77		0.01		
age	-0.02	0.01	-0.32	0.17		
sex	-0.15	0.29	-0.10	0.61		
emotional abuse	-0.04	0.03	-0.31	0.23		
emotional neglect	0.05	0.03	0.36	0.18		
physical neglect	0.14	0.06	0.56	0.04		
Step 3					0.43	0.27
constant	2.13	0.93		0.04		
age	-0.02	0.01	-0.31	0.27		
sex	-0.20	0.33	-0.14	0.54		
emotional abuse	-0.04	0.04	-0.28	0.32		
emotional neglect	0.03	0.05	0.25	0.49		
physical neglect	0.14	0.07	0.55	0.07		
HDRS1	0.01	0.03	0.09	0.73		
HDRS2	0.02	0.05	0.11	0.70		

HDRS= Hamilton depression rating scale at T1 (1) and T2 (2)

Age and sex had a significant impact on SAA levels. In particular, the first model assessing the influence of age and sex reached statistical significance ($F_{2,22}$=4.40, p=0.03). The second and third models including CTQ subscales and severity of depression, respectively did not prove to be significant ($F_{5,19}$=1.90, p=0.14 and $F_{7,17}$=1.81, p=0.15) (Table 7).

Age as well as sex had a statistically significant impact on the average measure of resistin levels. ($F_{2,22}$=7.57, p=0.00 for the first model). The model as a whole remained significant when CTQ scores were added ($F_{5,19}$=1.90, p=0.14), without any particular variable reaching significance. When severity of depression was added to the equation, the model was not significant any more ($F_{7,17}$=1.76, p=0.16) (Table 8).

Table 7. Results of the multiple regression analysis for SAA

	B	SE B	ß	p	R^2	adjusted R^2
Step 1					0.29	0.22
constant	6.35	4.28		0.15		
age	0.11	0.06	0.36	0.06		
sex	-3.69	1.80	-0.37	0.05		
Step 2					0.33	0.16
constant	4.35	5.50		0.44		
age	0.10	0.08	0.33	0.19		
sex	-4.00	2.04	-0.40	0.07		
emotional abuse	0.17	0.24	0.19	0.49		
emotional neglect	-0.09	0.23	-0.11	0.69		
physical neglect	0.25	0.45	0.15	0.59		
Step 3					0.42	0.18
constant	2.96	6.15		0.64		
age	0.04	0.09	0.13	0.66		
sex	-3.94	2.18	-0.40	0.09		
emotional abuse	0.11	0.24	0.12	0.66		
emotional neglect	-0.20	0.31	-0.24	0.53		
physical neglect	0.43	0.46	0.26	0.37		
HDRS1	0.27	0.19	0.35	0.18		
HDRS2	-0.07	0.32	-0.06	0.84		

HDRS= Hamilton depression rating scale at T1 (1) and T2 (2)

Table 8. Results of the multiple regression analysis for resistin

	B	SE B	ß	p	R^2	adjusted R^2
Step 1					0.41	0.35
constant	12.27	2.93		0.00		
age	-0.11	0.04	-0.46	0.01		
sex	3.07	1.23	0.41	0.02		
Step 2					0.45	0.31
constant	14.76	3.75		0.00		
age	-0.10	0.05	-0.41	0.08		
sex	2.47	1.39	0.33	0.09		
emotional abuse	0.07	0.16	0.11	0.66		
emotional neglect	-0.17	0.16	-0.26	0.31		
physical neglect	-0.04	0.31	-0.03	0.90		
Step 3					0.47	0.25
constant	13.49	4.45		0.01		
age	-0.10	0.06	-0.41	0.14		
sex	2.14	1.58	0.29	0.19		
emotional abuse	0.09	0.18	0.13	0.62		
emotional neglect	-0.26	0.22	-0.40	0.27		
physical neglect	-0.05	0.34	-0.04	0.89		
HDRS1	0.07	0.14	0.13	0.60		
HDRS2	0.11	0.23	0.13	0.63		

HDRS= Hamilton depression rating scale at T1 (1) and T2 (2)

Analysis of the potential impacts on CRP levels did not yield any significant results in the first ($F_{2,22}$=0.78, p=0.47, R^2=0.07, adjusted R^2=-0.02), second ($F_{5,19}$=1.50, p=0.24, R^2=0.28, adjusted R^2=0.10), or third model ($F_{7,17}$=1.10, p=0.41, R^2=0.31, adjusted R^2=0.03) of the regression analysis.

None of the variables assessed had an impact on adiponectin levels: ($F_{2,22}$=0.34, p=0.72, R^2=0.03, adjusted R^2=-0.06 for the first model, $F_{5,19}$=1.46, p=0.25, R^2=0.28, adjusted R^2=0.09 for the second model, and $F_{7,17}$=1.70, p=0.18, R^2=0.41, adjusted R^2=0.17 for the third model).

Similarly, TNF- α did not prove to be influenced by any of the variables that were evaluated here: ($F_{2,22}$=0.87, p=0.43, R^2=0.07, adjusted R^2=-0.01 for the first model, $F_{5,19}$=1.09, p=0.40, R^2=0.22, adjusted R^2=0.02 for the second model, and $F_{7,17}$=1.76, p=0.16, R^2=0.42, adjusted R^2=0.18 for the third model).

None of the variables, that were entered into any of the three steps of the regression analysis had an influence on levels of sE-selectin: ($F_{2,22}$=0.16, p=0.85, R^2=0.01, adjusted R^2=-0.08 for the first model, $F_{5,19}$=0.59, p=0.71, R^2=0.14, adjusted R^2=-0.09 for the second model, and $F_{7,17}$=0.66, p=0.70, R^2=0.21, adjusted R^2=-0.11 for the third model).

DISCUSSION

This study addressed the relationship between early life stress and clinically relevant proinflammatory markers in an inpatient population with major depression. The main findings of our investigation were that neglect and emotional maltreatment (i.e. emotional abuse and neglect) were the types of early life stress most commonly present in our sample, which is consistent with previous findings that early emotional adverse experiences are highly important to the development and maintenance of major depression (Chapman et al. 2004, Moskvina et al. 2007). The assessment of parental bonding mirrored these findings as nearly all patients experienced a parental style of affectionless control.

Past research has indicated that major depression is associated with increased levels of proinflammatory cytokines (Maes et al. 1990, Kim et al. 2007, Sperner-Unterweger 2005, Zeugmann et al. 2010, Zeugmann et al. 2012) possibly due to the accompanying induction of indoleamine 2,3-dioxygenase (IDO), an enzyme degrading tryptophan into kynurenine at the cost of serotonin (Muller & Schwarz 2007).

There is also an association between depression and cardiovascular disease (Frasure-Smith et al. 1995, Frasure-Smith & Lesperance 2006), which is probably due to depression and cardiovascular disease sharing inflammatory pathways that are involved directly in the processes that generate, initiate, maintain and worsen atherosclerosis and plaque rupture (Sack 2002, Paraskevas et al. 2008).

Depression and cardiovascular disease might result from prior stress related insult to the body (Miller & Blackwell 2006). This, of course, should have implications for the treatment of the patient groups affected, i.e. that physiological changes disadvantageous for general health should not be overseen during the treatment of a mood disorder.

We found physical neglect to be significantly associated with increased levels of fibrinogen. This is the first study showing that this coagulation marker is significantly influenced by early life experiences in adults suffering from major depression.

Our finding confirms the findings of Danese et al. (2007) of increased adult fibrinogen levels in participants that had been maltreated as children and we expanded them to the field of major depression.

In support of our finding, fibrinogen has been reported to be positively related to vital exhaustion resulting from chronic stress in teachers (Kudielka et al. 2008), and burnout in women (Toker et al. 2005) thereby indicating a presumable association between prolonged periods of stress and increment of this acute-phase protein. According to the schema-focused model of occupational stress and work dysfunctions (Bamber 2006) it is individuals with early maladaptive schema that gravitate towards occupations with similar dynamics to the toxic environments that created them. Those affected subsequently re-enact these early maladaptive schemas and their associated coping styles (Bamber & McMahon 2008). Thus, in an indirect manner the above mentioned studies draw attention to the fact that adverse childhood experiences can affect fibrinogen levels in adulthood and our study confirmed this in a more direct manner.

Considering the meaning of mild proinflammatory activation, increased fibrinogen levels have been found to predict and contribute to cardiovascular mortality (Kop et al. 2010).

It would be advantageous to investigate whether treatment strategies that are particularly targeted at reversing the consequences of adverse childhood experiences, such as schema therapy (Young 2006), might also reverse the putative long lasting psychophysiological effects of early life stress. Furthermore, Cox-2 inhibitors have been suggested for the treatment of at least some patients with major depression (Muller et al. 2006) and it might be of interest whether subgroups of patients such as the sample studied here would benefit from these compounds.

An important limitation to the current study is that it was conducted under naturalistic conditions. Nearly all patients had been receiving psychopharmacological treatment at admission to the clinic. From admission onwards all patients medicated and received psychotherapy (group or individual). Evidence considering putative immunoregulatory properties of antidepressants is available (e.g. Bah et al. 2011, Chavda et al. 2011) but not unequivocal (Haastrup et al. 2012). Psycho-

therapeutic interventions have been found to influence concentrations of inflammatory markers (e.g. Thornton et al. 2009), but there is only a very limited body of research in this area. However, owing to our study design, no conclusions can be drawn considering putative anti-inflammatory effects of the treatments applied. Furthermore, had there been any immuno-regulatory effects of the therapies, they would have been evenly spread as all our patients were all treated at all times of data assessment.

CONCLUSIONS

Altogether the topic of early life stress and subsequent immunomodulation is quite new and not well investigated so far. Our findings will hopefully trigger further research in this area, which will provide larger samples with complementing data. Considering depressive disorders, experiences of disturbed and abusive attachment often play a pivotal role in the development of this disease, the consequences of which remain present up to adulthood (e.g. in the form of maladaptive core beliefs). Since the mind and body are not separate entities, it is very likely that the echo of the past does not only resound on a psychological domain but spreads also to somatic areas, some evidence for which was provided here.

Acknowledgements

We thank Dr. Duncan George (Department of Psychiatry and Psychotherapy, Charité, Campus Benjamin Franklin – University Medicine Berlin, Germany) for reviewing the English language of this paper. We thank Prof. Nikolaus Marx (Department of Internal Medicine I, University Hospital Aachen, Germany) and Prof. Koenig (Department of Internal Medicine II and Cardiology, University of Ulm, Germany) for the measurement of the inflammatory markers.

Conflict of interest:

S. Zeugmann: None declared. A. Quante: None declared. N.Buehrsch: None declared. M.Bajbouj: None declared. I.Heuser: Bayer Health Care – consultant, Astra Zeneca – consultant; Novartis – consultant, GE Health Care – consultant. I.Anghelescu: None declared.

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