Circulating pro-inflammatory CD4posCD28null T cells are independently associated with cardiovascular disease in ESRD patients

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Abstract

Background. Cytomegalovirus seropositivity is associated with an increased risk for cardiovascular disease in end-stage renal disease (ESRD) patients. Circulating pro-inflammatory CD4posCD28null T cells are expanded in cytomegalovirus-seropositive ESRD patients and potentially could mediate atherosclerotic plaque instability and rupture.
Methods. In this study, we tested the hypothesis that increased numbers of circulating CD4posCD28null T cells may represent a risk factor for cardiovascular disease in ESRD patients. Prospectively collected data from 240 cytomegalovirus-seropositive stable ESRD patients were analysed.

Results. Traditional cardiovascular risk factors (age, smoking, hypercholesterolaemia and diabetes mellitus) and the percentage and absolute number of CD4posCD28null T cells were significantly associated with the presence of atherosclerotic disease, after univariate and multivariate statistical analysis. An ~2–3-fold increase in the prevalence of atherosclerotic disease was noted between patients with the highest and lowest number of CD4posCD28null cells. CD8posCD28null T-cell populations were also significantly expanded in cytomegalovirus-seropositive ESRD patients and closely correlated with the number of CD4posCD28null T cells. However, this cell population was not related to an increased prevalence of cardiovascular disease.

Conclusions. Cytomegalovirus-seropositive ESRD patients may have substantially increased numbers of circulating pro-inflammatory CD4posCD28null T cells that are independently associated with the presence of atherosclerotic disease. The expansion of these cells may therefore represent a novel non-traditional cardiovascular risk factor for ESRD patients.

Keywords: atherosclerosis; cytomegalovirus; inflammation; kidney; T cells

Introduction

Patients with end-stage renal disease (ESRD) carry a highly increased risk for cardiovascular disease [1]. Traditional risk factors like smoking, hypertension and hypercholesterolaemia can be identified but do not explain the full magnitude of the increment in risk [2]. In addition, treatment with statins has not resulted in a decreased cardiovascular mortality, indicating that other mechanisms of atherosclerotic disease are important [3–5]. Recently, we showed that cytomegalovirus (CMV) seropositivity is significantly associated with atherosclerotic disease in ESRD patients [6], as was previously shown in a number of studies including patients with normal renal function [7–10]. However, the association between CMV seropositivity and atherosclerosis is not unequivocal and seems most consistent when CMV seropositivity is considered as a risk factor for secondary atherosclerotic events [8]. Also, in animal models in which CMV is shown to be pro-atherogenic, aggravation of pre-existing atherosclerosis and not a primary CMV-induced atherosclerosis is observed [11,12]. In addition, the cellular immune response and not CMV infection per se seems responsible for the pro-atherogenic activity of CMV [11]. We recently showed that the relative and total numbers of a subset of circulating CD4-positive T cells without CD28 expression (CD4posCD28null cells) can be massively expanded up to 60% of total CD4 T cells, but only in CMV-seropositive ESRD patients [13]. In CMV-seronegative individuals, the frequency of CD4posCD28null cells was always <1% (on average 0.2%) of the total CD4 T cells. Upon further analysis, these cells showed a highly pro-inflammatory and cytotoxic profile [13,14]. In a series of studies, it was shown that this type of CD4-positive T cells is present in unstable atherosclerotic plaques and associated with an increased risk for recurrence of both acute coronary events and ischaemic stroke [15–18] [19]. Subsequently, human CD4posCD28null cells were shown to invade and cause apoptosis of vascular smooth muscle cells in the atherosclerotic plaque of a human carotid artery xenotransplant in a mouse [20]. Subclinical CMV re-activation seems more prevalent in ESRD patients, and rarely even CMV disease has been observed [21,22], which may be related to the uraemia-associated immune deficiency in these patients [23]. Therefore, one may hypothesize that frequent subclinical CMV re-activation in ESRD patients is the antigenic trigger that leads to expansion of the number of circulating CD4posCD28null cells, thereby increasing the risk for progressive inflammation of atherosclerotic plaques. This hypothesis obviates the need for CMV antigen within the atherosclerotic plaque, which has not been convincingly documented thus far [12]. Moreover, it would offer an (additional) explanation and a novel non-traditional risk factor for the high prevalence of atherosclerotic disease in ESRD patients. However, to date, there are no studies that have investigated the relation between CD4posCD28null cells and atherosclerotic disease in ESRD patients. In this study, we tested the hypothesis that an expanded population of circulating CD4posCD28null cells in CMV-seropositive ESRD patients is independently associated with the presence of atherosclerotic disease.

Materials and methods

Patient

Patient data were collected in the period between June 2007 and September 2009. CMV-seropositive patients with ESRD, defined as a glomerular filtration rate of 15 mL/min or less with or without renal replacement therapy, were included prior to renal transplantation. The referring area of the renal transplantation department of the Erasmus Medical Center, consists of the southeast part of the Netherlands and contains 3 million inhabitants, with an average CMV seropositivity of 70% [6]. First and second generation immigrants from outside Western Europe were classified as being from non-Western European origin. Patients included gave informed consent, and the local medical ethical committee approved the study. It was conducted according to the principles of the Declaration of Helsinki and in compliance with International Conference on Harmonization/Good Clinical Practice regulations.

Clinical evaluation

All patients referred to our outpatient clinic were screened for the presence of symptomatic coronary artery disease. Myocardial infarction (MI) reported in the medical history was confirmed if the medical record review demonstrated symptoms consistent with MI and the presence of either diagnostic ECG changes or cardiac enzymes. Evidence for cardiac ischaemia at the time of pre-operative evaluation was obtained by graded exercise on a bicycle, or a dobutamine stress echocardiography was performed. These procedures were followed by coronary angiography when changes on the ECG were consistent with cardiac ischaemia. Signs of coronary atherosclerotic disease on coronary angiography were noted as either being absent or present. Symptomatic carotid artery disease was considered to be present when an atherosclerotic diseased carotid artery
Table 1. Demographic and clinical characteristics of CMV-seropositive patients with end-stage renal disease

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Number of patients</th>
<th>Age (median and range in years)</th>
<th>Male</th>
<th>Non-Western European origina</th>
<th>Previous renal transplant</th>
<th>Not receiving dialysis treatment</th>
<th>History of atherosclerotic disease</th>
<th>Cardiovascular</th>
<th>Cerebrovascular</th>
<th>Aorta/Peripheral arteries</th>
<th>Underlying kidney disease</th>
<th>Hypertensive nephropathy</th>
<th>Primary glomerulopathy</th>
<th>Diabetic nephropathy</th>
<th>Polycystic kidney disease</th>
<th>Other</th>
<th>Unknown</th>
<th>Prevalence of risk factors for atherosclerosisa</th>
<th>CRP concentration mg/l (median and range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>240</td>
<td>57 (20–86)</td>
<td>64.2%</td>
<td>41.7%</td>
<td>18.3%</td>
<td>22.5%</td>
<td>35.0%</td>
<td>23.3%</td>
<td>11.0%</td>
<td>11.0%</td>
<td>9.2%</td>
<td>19.0%</td>
<td>5.7%</td>
<td>91.7%</td>
<td>58.1%</td>
<td>37.3%</td>
<td>29.8%</td>
<td>3 (1–96)</td>
<td></td>
</tr>
</tbody>
</table>

aFirst and second generation immigrants from outside Western Europe were classified as being from non-Western European origin. A patient who stopped smoking >10 years ago was considered not to have smoking as a risk factor. Diabetes was diagnosed if a patient was taking insulin or oral hypoglycaemic agents, or had previously received such treatment and was currently using dietary modification to control the condition. A patient was considered to have hyperlipidaemia if he or she had a serum cholesterol value of >6.5 mmol/L and/or was receiving antihyperlipidaemic treatment. A patient was considered to have hypertension if he or she had received the diagnosis, or was being treated with antihypertensive medications at the time of evaluation.

had been documented by angiography or ultrasonography, in most cases after a cerebrovascular accident. A cerebrovascular accident because of atherosclerosis was considered to be present if confirmed by a computed tomography scan of the brain.

Atherosclerotic disease of the large peripheral arteries, including the aorta, was documented as being present if confirmed by angiography or aortography. The latter was performed because of symptoms of claudiciatio intermittens, abnormalities noted on physical examination that indicated peripheral arterial stenosis or occlusion or aneurysmatic enlargement of the aorta.

Risk factors

Traditional risk factors for atherosclerotic disease considered in this study included age, male sex, smoking, diabetes, hyperlipidaemia and hypertension. A history of past and current smoking was obtained. A patient who stopped smoking >10 years ago was considered not to have smoking as a risk factor. A patient was considered to have diabetes if he or she was taking insulin or oral hypoglycaemic agents, or had previously received such treatment and was currently using dietary modification to control the condition. A patient was considered to have hyperlipidaemia if he or she had a serum cholesterol value of >6.5 mmol/L and/or was receiving antihyperlipidaemic treatment. A patient was considered to have hypertension if he or she had received the diagnosis, or was being treated with antihypertensive medications at the time of evaluation.

CMV serology and CRP level

Serum immunoglobulin G (IgG) antibodies to CMV were measured with an enzyme immunoassay (Biomerieux, VIDAS, Lyon, France) and expressed as arbitrary units/millilitre (AU/ml). Following the manufacturers’ guidelines, a test result exceeding 6 AU/ml was considered positive for the presence of CMV-specific IgG antibodies. The C-reactive protein (CRP) level was measured with a fluorescence polarization immunoassay (TDxFLEx analyser; Abbott Labs). 95% of healthy individuals had a CRP level of 8 mg/L. The lower limit of detection was 1 mg/L, and values below this limit (8% of all data) were counted as blanks in the statistical analysis.

Quantification of CD28null T cells

Peripheral blood mononuclear cells were isolated from heparinized peripheral blood samples. The identification of T lymphocytes expressing CD4 or CD8 and lacking the CD28 molecule on the cell surface was done by fluorescence-activated cell sorting (FACS) analysis, as has been described previously in detail [13]. The number of CD4posCD28null T cells was expressed as percentage of the total CD4 T cells and as the total number of cells per millilitre blood. The percentage and absolute numbers of circulating CD8posCD28null T cells are also increased in CMV-positive individuals. However, in contrast to the CD4posCD28null population, the CMV-seronegative individuals already have an average of 20% CD8posCD28null T cells [14]. To investigate whether the relation of CD4posCD28null cells with atherosclerotic disease is unique, the CD8posCD28null cells were also included in the analysis. Age- and sex-matched CMV-seronegative ESRD patients were included in the analysis to show the impact of CMV on the expansion of CD28null T lymphocytes. Both CD4posCD28pos and CD4posCD28null T cell subsets were analysed for expression of interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α) after polyclonal stimulation, as described previously in detail [14].

Statistical analysis

Categorical data were analysed by the χ² test. All statistical tests were two-sided. All relevant variables were first examined in a univariate analysis for the relation with the presence of atherosclerotic disease. The results of the multivariate logistic regression analysis were confirmed with forward and backward modelling. To analyse the association with underlying renal disease, the patients were grouped into two categories: hypertensive nephropathy and primary renal disease. The CRP levels were log-transformed before adding them as a covariate in the model. Differences between groups were analysed with the Student’s t-test when the variable was normally distributed and otherwise by the Mann–Whitney test. The SPSS software version 15.0 was used for all statistical tests.

Results

Clinical characteristics

Two hundred and forty CMV-seropositive patients with ESRD were included in the study. The clinical characteristics are shown in Table 1 and reflect the high burden of atherosclerotic disease in this group of patients, as more than one-third of all patients had a medical history of atherosclerotic disease. The very high prevalence of hypertension is typical for an ESRD patient population.

CD4posCD28null cells are significantly expanded in ESRD patients with atherosclerotic disease

The percentage and number of CD4posCD28null cells were significantly higher in patients with documented atherosclerotic disease in their medical history (5.7% vs 9.0% and 20 vs 36 × 10⁴ cells/mL, Figure 1A and C). The presence of CD28null cells in the CD4pos and CD8pos T-cell populations (CD4posCD28null cells and CD8CD28null cells) was significantly correlated (Spearman's rho 0.66, P < 0.01 for percentages, rho 0.72, P < 0.01 for absolute cell numbers). The median percentage of CD8CD28null cells was slightly but statistically significant increased in patients with atherosclerotic disease (53.3% vs 49.2%,
However, the absolute number of CD8posCD28null T cell was identical for ESRD patient's groups with or without atherosclerotic disease (107 × 10^4 cells/ml, Figure 1D).

The control CMV-seronegative ESRD patients showed, as expected, a very low number of CD4posCD28null cells (median 0.2% of CD4 T cells and 1.3 × 10^4 cells/ml, P < 0.0001 compared to CMV-seropositive patients) and a substantially lower number of CD8posCD28null cells (median 17% of CD8 T cells and 23 × 10^4 cells/ml, P < 0.0001 compared to CMV-seropositive patients).

Unadjusted for other risk factors, a significant linear relation was observed between the percentage of ESRD patients with cardiovascular disease and both the percentage and the absolute number of CD4posCD28null cells (Figure 2). Approximately, a 2–3-fold increased prevalence of cardiovascular disease was present between ESRD patients with the highest and lowest number of CD4posCD28null cells.

The percentage of IFN-γ- and TNF-α-producing cells in the CD4posCD28null T-cell subset was significantly higher compared to the CD4posCD28pos T-cell subset (37% vs 18% P < 0.01 for IFN-γ and 50% vs 38% for TNF-α; P < 0.001). However, similar percentages were found for patients with or without cardiovascular disease (Figure 3).

![Figure 1](https://academic.oup.com/ndt/article-abstract/25/11/3640/1899279/3643)

**Fig. 1.** The median percentage of CD28null cells within the total CD4 or CD8 T-cell population (% CD4posCD28null T cells and % CD8posCD28null T cells in A and B) and the absolute number of CD4posCD28null T cells and CD8posCD28null T cells (C and D) are shown for CMV-seronegative patients (CMVneg, n = 150) and CMV-seropositive patients with or without cardiovascular disease (CMVpos-CVDneg, n = 156 and CMVpos-CVDpos, n = 84). The whiskers indicate the 5–95% interval of the data.

![Figure 2](https://academic.oup.com/ndt/article-abstract/25/11/3640/1899279/3643)

**Fig. 2.** The prevalence of cardiovascular disease (CVD) in ESRD patients stratified for the percentage (A) of CD28null cells within the total CD4 T-cell population (0–5%; n = 95, 5–10%; n = 42, 10–15%; n = 29, 15–20%; n = 23, 20–25%; n = 15, 25–30%; n = 16) or the total number (B) of CD4posCD28null T cells (0–5; n = 42, 5–15; n = 42, 15–25; n = 33, 25–35; n = 22, 35–45; n = 23, 45–55; n = 25, >55; n = 44).
Traditional risk factors and CD4posCD28null cells are associated with atherosclerotic disease

All traditional risk factors for atherosclerotic disease, serum CRP concentration, percentage and total number of CD4posCD28null cells, and possible confounders were univariately tested for their relation with the presence of atherosclerotic disease (Table 2). The univariate and multivariate analysis showed that both the percentage and the absolute numbers of CD4posCD28null cells (Table 2) were significantly associated with the presence of atherosclerotic disease. The odds ratios for percentage and absolute number of CD4posCD28null cells indicated a similar increase in risk for the presence of atherosclerotic disease (per percent and $1 \times 10^4$ cells/ml) as was found with the results from the unadjusted analysis (Figure 2). In the multivariate analysis, patient's age and traditional risk factor like smoking, diabetes mellitus and hypercholesterolaemia had significantly elevated odds ratios. We did not identify statistically significant interactions between CD4posCD28null cells and other risk factors. Both the percentage and absolute number of CD8CD28null cells were not related to the presence of atherosclerotic disease after multivariate analysis (data not shown).

Remarkably, the CRP concentration was not significantly associated with cardiovascular disease anymore in the multivariate analysis. No statistically significant correlation between CD4posCD28null cells and serum CRP levels (Spearman's rho 0.1, $P = 0.11$) was found.

Discussion

The results of this study show for the first time that expansion of inflammatory CD4posCD28null cells in CMV-seropositive patients is independently associated with the presence of atherosclerotic disease in ESRD patients. Therefore, the findings of this study indicate that circulating

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Table 2. Univariate and multivariate analysis of clinical and demographic parameters in association with a positive history of atherosclerotic disease in patients with end-stage renal disease

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>P-value</th>
<th>Multivariate analysis with % CD4posCD28null cells</th>
<th>P-value</th>
<th>Multivariate analysis with CD4posCD28null cells/ml</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.21 (0.68–2.12)</td>
<td>0.55</td>
<td>2.35 (0.92–5.99)</td>
<td>0.07</td>
<td>2.21 (0.85–5.72)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.06 (1.04–1.09)</td>
<td>&lt;0.001</td>
<td>1.08 (1.04–1.12)</td>
<td>&lt;0.001</td>
<td>1.08 (1.04–1.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis treatment</td>
<td>0.98 (0.69–1.39)</td>
<td>0.86</td>
<td>1.76 (0.96–3.24)</td>
<td>0.06</td>
<td>1.66 (0.88–3.13)</td>
<td>0.11</td>
</tr>
<tr>
<td>Non-Western European background</td>
<td>1.23 (0.71–2.11)</td>
<td>0.56</td>
<td>2.26 (0.87–5.90)</td>
<td>0.09</td>
<td>2.76 (1.04–3.33)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.74 (1.06–2.85)</td>
<td>0.02</td>
<td>2.46 (0.98–6.17)</td>
<td>0.05</td>
<td>2.30 (0.94–5.67)</td>
<td>0.06</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.28 (1.23–4.21)</td>
<td>0.007</td>
<td>3.10 (1.22–7.85)</td>
<td>0.01</td>
<td>3.23 (1.26–8.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>5.62 (2.90–10.91)</td>
<td>&lt;0.001</td>
<td>4.75 (1.71–13.22)</td>
<td>0.003</td>
<td>4.93 (1.74–13.92)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.90 (0.34–2.38)</td>
<td>0.83</td>
<td>0.38 (0.06–2.61)</td>
<td>0.32</td>
<td>0.35 (0.04–2.59)</td>
<td>0.30</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>2.30 (1.25–4.22)</td>
<td>0.004</td>
<td>1.38 (0.68–2.80)</td>
<td>0.36</td>
<td>1.37 (0.66–2.87)</td>
<td>0.39</td>
</tr>
<tr>
<td>Underlying kidney disease</td>
<td>0.87 (0.77–0.98)</td>
<td>0.05</td>
<td>1.00 (0.81–1.24)</td>
<td>0.97</td>
<td>1.02 (0.83–1.27)</td>
<td>0.81</td>
</tr>
<tr>
<td>% CD4posCD28null T cells</td>
<td>1.03 (1.00–1.06)</td>
<td>0.009</td>
<td>1.04 (1.00–1.08)</td>
<td>0.04</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CD4posCD28null T cells/ml</td>
<td>1.01 (1.00–1.01)</td>
<td>0.03</td>
<td>–</td>
<td>–</td>
<td>1.01 (1.00–1.02)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*First and second generation immigrants from outside Western Europe were classified as being from non-Western European origin. Odds ratios (OR) were calculated for the increase of age per year, of C-reactive protein per milligram/litre and of CD4posCD28null T cells per percent and 10 000 cells/ml. All other ORs with confidence interval (CI) were calculated for the presence of the variable as indicated. The $R^2$ of the model including the % CD4posCD28null T cells was 0.49, and $R^2$ of the model including the CD4posCD28null T cells/ml was 0.51.
CD4posCD28null cells may act as a new non-traditional risk factor in ESRD patients.

A number of studies have been published in recent years that have indicated that the population of CD4posCD28null cells is expanded in patients with atherosclerotic disease and associated with recurrence of a cardiovascular event [19]. Subsequently, a possible pathogenetic mechanism was identified, as this particular cell population is capable of infiltrating and destabilizing atherosclerotic plaques [20]. Given this proposed mechanism of action of CD4posCD28null cells, their numbers should associate with vascular events and not necessarily with presence of atherosclerotic disease, as was shown in this study. However, this is largely a paradox because the presence of atherosclerotic disease was in most patients defined by a medical history of cardio- and cerebrovascular events.

The expansion of CD4posCD28null cells is without doubt directly related to CMV seropositivity as the numbers of this particular cell population almost never exceed 1% in CMV-seronegative individuals [13,24]. In addition, proliferation of expanded CD4posCD28null cells was only observed in response to CMV antigens [24]. The loss of CD28 cell surface expression on antigen-specific T cells is not exclusive for CMV infection [25]. However, a sustained expansion of CD28null cells to an average 3% of the total CD4-positive T cells in healthy individuals is only observed in response to CMV infection [13]. The average size of the CD4posCD28null cells population is even more enlarged in ESRD patients [13]. This shift in T-cell phenotype coincides with the development of CD4 lymphocytopenia, which is strongly related with the progressive loss of renal function [26]. The uraemia-associated immune deficiency of ESRD patients [23] may allow for frequent subclinical reactivation of CMV, eventually leading to continuous expansion of the CMV antigen-specific T cells. A similar situation, although unproven, may be present in immunocomprised HIV patients and patients with rheumatoid arthritis. In both patient groups, an increased number of circulating CD4posCD28null cells has been reported as well as an increased prevalence of atherosclerotic disease [27–31].

The results of the present study are in accordance with previous studies that have identified CMV as a risk factor for atherosclerotic disease [8]. As such, we have extended these observations by identifying the CMV-related expansion of CD4posCD28null cells as a pathophysiologic mechanism that may underlie this association. Of particular interest is the finding that changes in the immune system in the very old, similar to what can be observed in ESRD patients (low CD4 T-cell count combined with expansion of the CD28null T-cell population), predicts mortality [32,33]. In addition, shortening of telomere length in human CD8CD28null T cells is highly related to CMV seropositivity [34], and this phenomenon is most evidently observed in coronary heart disease patients [35]. Therefore, evidence is accumulating that the CMV-induced alterations in the T-cell system are clinically relevant to atherosclerosis.

However, the possibility cannot be ruled out that our result is biased by unidentified confounders, and CD4posCD28null cells are only an epiphenomenon. For instance, it is possible that an inflammatory response associated with atherosclerotic disease is causing expansion of CD4posCD28null cells. This is not only hypothetical, as a pro-inflammatory environment may lead to activation of NF-kappaB, by e.g. tumour necrosis factor-alpha, which induces the immediate–early antigen required for CMV replication [36]. For this reason, we included CRP as a covariate in our model but were unable to identify a significant relationship with expansion of CD4posCD28null cells. In fact, after multivariate analysis, the CRP level was no longer significantly associated with atherosclerotic disease. However, in a previous study, we observed the highest prevalence of atherosclerotic disease in ESRD patients with high CRP levels and CMV seropositivity. Therefore, an inflammatory response may exacerbate the effects of CMV on the severity of cardiovascular disease. In this respect, the significant association of non-Western European ethnicity with atherosclerotic disease in the multivariate analysis is of interest. Although highly hypothetical, this may be related to the higher exposure to infectious diseases (reflected by the almost 100% CMV seropositivity in these patients [6]) causing more frequent episodes of inflammation.

We did not find a significant association between expansion of CD8CD28null cells and the presence of atherosclerotic disease, although the numbers of CD28null cells in both CD4 and CD8 T-cell populations are highly correlated. These findings are in support of the conclusion that expanded CD4posCD28null cells may indeed be the culprit cell population for the CMV-related increase in atherosclerotic disease.

An intriguing observation is the large variation in expansion of CD4posCD28null cells in CMV-seropositive ESRD patients, which is independent of dialysis treatment, and has not been sufficiently explained thus far. In addition, it is not known whether an expanded CD4posCD28null cell population in ESRD patients can be reduced again by, e.g. pharmacological interventions. In patients with unstable angina, statin therapy was associated with reduction of CD4posCD28null cell numbers [37,38]. Given the negative clinical impact of the expansion of CD4posCD28null cells in ESRD patients, both on atherosclerotic disease and erythropoiesis [14], an exploration of the factors involved in CD4posCD28null T-cell homeostasis seems warranted.

Conflict of interest statement. None declared.

References


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