ORIGINAL ARTICLE

Levels of procalcitonin, C-reactive protein and neopterin in patients with advanced HIV-1 infection

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Objectives. To compare the value of procalcitonin, C-reactive protein (CRP) and neopterin as indicators of immune deficiency, co-infection, efficacy of treatment, and disease progression, in patients with advanced HIV-1 infection.

Design. Cross-sectional, investigating baseline blood measurements and clinical observations in 82 HIV-positive patients divided into an antiretroviral treatment (ART) group and an ART-naïve group.

Setting. Secondary general hospital in Pretoria.

Results. Procalcitonin and CRP levels showed no significant differences between the ART and ART-naïve groups, and no correlations with CD4 counts or viral loads. CRP levels were significantly higher with TB co-infection ($p<0.05$). Neopterin levels were raised above normal in 92% of the ART-naïve group and in 75% of the ART group. The levels were significantly higher ($p<0.05$) in the ART- naïve group. Negative correlations were found between neopterin and CD4 counts for the total patient group ($r=-0.482$; $p<0.001$). Neopterin was significantly ($p<0.05$) higher in the HIV/TB co-infection group than in those without TB. Higher neopterin levels at baseline were associated with a decline in CD4 counts over the ensuing 6-month period, and patients with higher baseline neopterin levels developed more complications over the 6-month period.

Conclusions. Compared with procalcitonin and CRP, neopterin appears to be associated with the degree of immunodeficiency and of co-infection with TB. Neopterin levels may be investigated further as a measure of disease progression or treatment response.

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Procalcitonin, C-reactive protein (CRP) and neopterin are three of the markers most commonly used, with varying degrees of success, as diagnostic or prognostic indicators to monitor disease progression and to estimate the efficacy of therapeutic interventions in infectious diseases and non-infectious inflammatory conditions. All three are, to a lesser or greater extent, used among HIV-positive patients.

Procalcitonin is the pro-hormone of calcitonin. In normal conditions, transcription of the procalcitonin gene occurs in the C-cells of the thyroid under conditions of hypercalcaemia and neoplastic disease.[1] However, in the presence of bacterial infection or endotoxins, virtually all cells produce calcitonin precursors.[1] Recent indications are that, in infectious or inflammatory conditions, procalcitonin may in fact be considered an acute phase reactant, with the liver being the major source of procalcitonin.[2] Procalcitonin levels increase in certain pro-inflammatory conditions, especially bacterial infections, but are thought not to show significant increases with viral and non-infectious inflammatory conditions.[3] The levels are often used to differentiate between patients with sepsis and those with systemic inflammatory response syndrome (SIRS).[4] Procalcitonin levels have been recommended for distinguishing between bacterial and non-bacterial infections, and therefore as a guideline in the prescription of antibiotics.[5,6] One disadvantage in the use of procalcitonin is that the levels in healthy individuals are below the reliable detection limit (10 pg/ml) of most clinical assays.

C-reactive protein is an acute-phase protein, and its levels are upregulated in viral, bacterial and fungal infections, as well as in non-infectious inflammatory conditions. The cytokine profile found with raised CRP levels is predominantly pro-inflammatory, and CRP levels are often used as a non-specific indicator of inflammatory activity, irrespective of the cause.[7] The levels of CRP in bacterial and viral infections differ, and high levels (e.g. >100 mg/l) can be found with bacterial infections, while lower levels (usually <10 mg/l) are more commonly associated with viral infections.[8] As an acute-phase reactant, macrophage- and perhaps adipocyte-derived IL-6 is a major stimulant for the production of CRP, and liver failure is the major cause for a decline in CRP synthesis.[9,10]

Neopterin (6-D-erythro-hydroxy propyl pteridine) is a catabolic product of the purine nucleotide guanosine triphosphate. Neopterin is produced in macrophages from guanosine 5'-triphosphate (GTP) which is cleaved by GTP-cyclohydrolase 1 to 7,8-dihydroneopterin triphosphate, followed by conversion of 7,8-dihydroneopterin triphosphate

to neopterin and 7,8-dihydroneopterin under the influence of phosphatases.[11] GTP-cyclohydrolase 1 is stimulated, predominantly, by T-helper cell type-1 derived interferon-g, but co-stimulation by tumour necrosis factor alpha may contribute.[11] Neopterin is used as indicator of both macrophage function and cell-mediated immunity. When cell-mediated immunity dominates, circulating neopterin levels are usually high and, when humoral immunity dominates, neopterin levels are low.[11] Increased neopterin levels are found with viral infections, intracellular bacterial infections, intracellular parasites, a number of auto-immune diseases, malignancies, rheumatoid arthritis, systemic lupus erythromatosus, acute cellular graft rejection or graft-v.-host disease, and in almost every condition where cellular immunity dominates.[12,13] In HIV-1 infection, serum neopterin has been described as an immune activation marker and predictor of disease progression.[14]

In HIV/AIDS, plasma HIV-1 RNA concentration reveals the degree of viral replication, and CD4 counts reflect the degree of immune deficiency and, it is speculated, end-organ damage. The outcome is, however, largely influenced by the co-existence of other complications, especially co-infection with TB. Although viral load and CD4 counts are considered the diagnostic gold standards for HIV, soluble markers may add valuable information about immune activation status and prognosis. In addition, cost-effective reliable serum markers would be of benefit in resource-limited settings where restrictions are placed on the frequency of laboratory investigations such as viral loads. The aim of this investigation was to compare the associations of procalcitonin, C-reactive protein and neopterin and measures of HIV disease status and co-infection with TB.

Methods

HIV-positive outpatients were randomly recruited from the Immunology Clinic at the Kalafong Hospital, Pretoria. The study took place during 2010 - 2011, and patients were followed-up 6 months after baseline, wherever possible.

Informed consent was obtained from 82 adult patients who were attending the clinic on a Friday, who freely gave informed consent to take part, and who were not ruled out by the exclusion criteria. Exclusion criteria included patients <18 years of age, patients with CD4 counts >400 cells/µl, patients on antiretroviral treatment (ART) for <2 months, treatment defaulters from the ART group and, for the ART-naïve group, patients previously on any ART. Ethical approval was obtained from the Faculty of Health Sciences Research and Ethics Committee, University of Pretoria.

The patients were firstly divided into a group on active ART (*N*=57) and a group not on ART (ART-naïve; *N*=25). The ART group was further subdivided into groups depending on their time on treatment prior to baseline investigation (2 months - 1 year; 1 - 2 years, and >2 years). At the 6-month follow-up, patients were subdivided into 2 groups according to baseline neopterin levels, and the groups were compared in terms of the CD4 counts and development of complications diagnosed by the attending physician and confirmed by the specialist involved in the study.

Blood specimens collected at baseline were centrifuged on site; plasma aliquots were stored at -70°C until analysis. Procalcitonin (RayBiotech Inc., USA) and neopterin (Immuno-Biological Laboratories Inc., USA) were measured by commercial enzyme-linked immune-absorbent assay (ELISA) kits. CRP and other routine blood investigations (CD4 count, WBC count, haemoglobin etc.) at baseline were determined according to standard procedures of the National Health Laboratory Service (NHLS), and results were extracted from the laboratory reports and patient files.

Student's *t*-test and nonparametric Mann-Whitney U-test were used to determine group differences. Kruskal-Wallis one-Way ANOVA indicated variance across multiple groups. Correlations were determined by regression analysis and Spearman rank correlation co-efficient. Statistical analysis was performed using NCSS/PASS (Hintze J 2001) software, and all testing was done at a significance level <0.05 unless otherwise specified.

Table 1. Patient demographic information at baseline

	ART	ART-naïve
N	57	25
Females	35 (61.4%)	15 (60%)
Age (years)	36.6±8.2	36.8±10.8
Race	57 black	25 black
BMI	22.6±5.0	21.2±3.5
Married	10 (17.5%)	7 (28%)
Employed	22 (38.6%)	12 (48%)
Alcohol (number of patients)	3 (5.3%)	3 (12%)
Smoking (number of patients)	9 (15.8%)	5 (20%)
Average months on treatment	13.6±16.2 (2 - 63)	-
TB positive at baseline	10 (17.5%)	8 (32%)

Table 2. Comparison of baseline blood measurements for the two groups

	ART	ART-naïve	*p*-value
Procalcitonin (pg/ml)	13.2±3.3	12.9±1.5	0.767
Neopterin (nmol/l)	39.5±38.9	64.4±39.4	0.001*
CRP (mg/l)	25.3±38.5	34.9±82.9	0.567
CD4 count (cells/µl)	288.2±196.4	157.5±181.9	0.027*
Viral load (log_{10} copies/ml)	2.4±0.9	3.6±1.7	0.005*
Red cell count (x10^{12}/l)	3.6±0.5	3.9±0.7	0.048*
Haemoglobin (g/dl)	14.2±15.2	11.1±2.0	0.345
White cell count (x10^9/l)	4.9±1.5	5.7±2.8	0.107
Neutrophils (x10^9/l)	2.7±1.2	3.8±2.7	0.026*
Lymphocytes (x10^9/l)	1.6±0.8	1.4±0.8	0.211
CD4 % of lymphocytes	17.4±7.6	9.2±7.3	0.0006*

Note: Viral load measured within 2 months of baseline (*p<0.05; mean±SD).

Table 3. Comparisons for patients who were followed up after 6 months

	Complications after 6 months	No complications after 6 months
N	29 (61.7%)	18 (38.3%)
ART	12 (41.4%)	15 (83.3%)
Baseline CD4 count (cells/µl)	237.0	327.7
6 month CD4 count (cells/µl)	232.5	325.1
Baseline viral load (log_{10} copies/ml)	2.34±0.9	2.3±1.0
Baseline CRP (mg/l)	43.2±87.4	9.5±0.7
Baseline neopterin (nmol/l)	53.9±33.9	10.8±7.6
Baseline PCT (pg/ml)	13.7±4.5	12.6±0.43

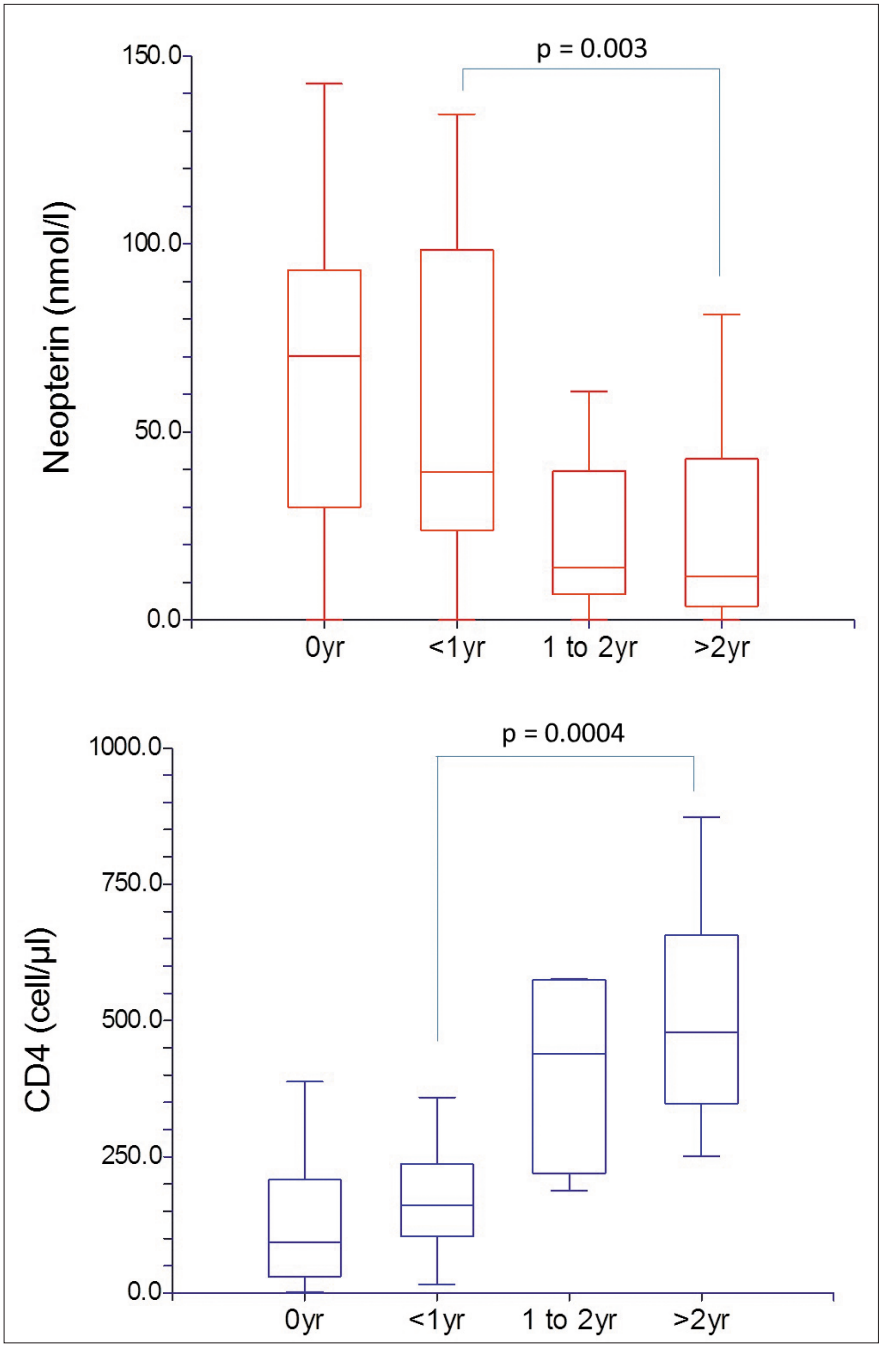

Fig. 1. Box plots illustrating neopterin and CD4 levels for patients after 0 years (n=25), <1 year (n=30), 1 - 2 years (n=10) and >2 years (n=10) on ART.

Results

The demographic profiles for the patient groups are presented in Table 1. The 2 groups were comparable in age, body mass index (BMI), gender distribution, race and employment status. Results of the baseline blood measurements and the comparison between the ART and ART-naïve groups are presented in Table 2. Neopterin levels were significantly higher (p=0.0096) in the ART-naïve group than in the ART group. Negative correlations were found between neopterin and CD4 counts for the total group of patients (r=-0.482; p<0.0001; N=82), as well as for the ART group (r=-0.451; p=0.0045; n=57). Neopterin also correlated negatively with haemoglobin levels for the total patient group (p=-0.597; p<0.0001; N=82).

Six months after the baseline measurements, 47 of the original 82 patients were still available and could be followed up with regard to CD4 counts and the development of complications. A comparison between patients with complications and those without complications, at baseline and at follow-up, is shown in Table 3. Additional complications at follow-up consisted of TB (n=6, 2 of whom had extrapulmonary disease); pneumonia (n=5); severe lymphadenopathy (n=4); cardiac/renal disease (n=4) and haematological complications such as anaemia, thrombocytosis or neutrophilia (n=10).

The relationship between neopterin and CD4 counts over the 6-month period following the baseline assessments was examined. Patients who developed additional complications, stopped taking anti-retroviral drugs or ART-naïve patients who started ART during this period were excluded. Seven patients stopped ART over this period; the reasons included non-compliance and drug side-effects. This cessation resulted in a drastic decline in sample sizes, i.e. 11 patients (8 on ART) had a decrease, and 9 (all on ART) had an increase in CD4 over the period. Mean baseline neopterin was significantly higher in the patients whose CD4 counts were decreased at follow-up (35.09 v. 10.82 nmol/l; p=0.035). In the group whose CD4 counts decreased over the 6-month period, baseline neopterin levels correlated negatively with both baseline CD4 count (r=-0.68; p=0.03) and follow-up CD4 count (r=-0.58; p=0.07).

As shown in Fig. 1, the patients were subdivided into groups according to the period of time they had been on treatment prior to the baseline investigations. Analysis

of variance showed that neopterin levels were significantly ($p<0.01$) lower and CD4 counts significantly higher ($p<0.001$) in the patients who had been on treatment >1 year.

Discussion

This study examined the associations of 3 laboratory markers of disease in HIV-positive patients. The key findings are that neopterin is more strongly associated with the degree of immunodeficiency and of co-infection with TB than CRP or procalcitonin. Higher neopterin levels at baseline were associated with a decline in CD4 counts and the development of more complications over the ensuing 6-month period.

Limitations of this study include the fact that not all patients could be traced for the 6-months follow-up, that the groups became progressively smaller as patients who had a change in treatment over this period were excluded from the statistical comparisons, and that disease progression could only be estimated from CD4 counts and not viral loads.

The results of this study suggest that CRP levels are not specifically associated with immune deficiency, the effects of ART, or disease progression. These results are in agreement with those of a study in India in which CRP measurement in HIV-positive patients was found neither to be of value as diagnostic aid nor as prognostic marker in HIV/AIDS.[15] However, in view of the fact that CRP levels in HIV-positive individuals are generally significantly lower in viral than in bacterial infection, significantly raised levels of CRP could be an indication to investigate for a possible co-infection, keeping in mind that other conditions marked by a pronounced pro-inflammatory response can also lead to increases in the levels of CRP. This finding is in line with the results of a South African study by Wilson *et al.* who showed that normal CRP levels, in combination with clinical evaluation, could be useful to rule out TB in populations with a high prevalence of HIV.[16]

Procalcitonin (PCT) is known for its increase in bacterial infections and is used by some to differentiate between viral and bacterial infections.[17] One explanation as to why procalcitonin levels remain low in purely viral infections is based on the fact that the production of PCT is primarily stimulated by tumour necrosis factor. It is suggested that increases in procalcitonin do not occur with viral infections because alpha interferon, synthesised as a result of viral infections, inhibits synthesis of tumour necrosis factor.[1] Should this be true, the question remains whether procalcitonin would be of much use for the detection of bacterial co-infection in HIV-positive patients. In developing countries such as South Africa, co-infections with TB and other bacterial infections in HIV-positive individuals are common – even major sources of morbidity and mortality – especially at CD4 counts <200 cells/µl. The level of circulating PCT in normal healthy individuals is generally below the limit of detection (10 pg/ml) of most clinical assays.[18] According to sensitive research assays, the normal level for plasma/serum PCT is 33±3 pg/ml.[1] The analytical sensitivity for the assay of this study was typically below 30 pg/ml and, from linear extrapolation, individual PCT levels were all >10 pg/ml. However, the mean PCT levels for the total group of patients were normal, with no significant difference between the ART and ART-naïve groups, and no significant correlations between PCT and CD4 counts or viral loads. Although the value of PCT as a reliable marker of active TB has on occasion been questioned,[19] the overriding assumption is that PCT is indeed a valuable marker of *Mycobacterium tuberculosis* in non-immunocompromised patients.[20] The procalcitonin findings of this study are in line with studies that showed suppression of the procalcitonin response in HIV-positive individuals.[20,21] Although some diagnostic and prognostic value for the measurement of PCT in HIV/TB-co-infection has been described in a South African study, only 58% of their HIV-positive patients with TB had PCT levels marginally above 100 pg/ml.[22] This is, in view of better performing markers, not adequate for clinical use in individual patients. Although procalcitonin induction in HIV-positive individuals is known to occur in sepsis, and reports exist of significant increases in procalcitonin in pneumococcal and a number of other non-viral infections,[23] it would appear that secondary infections in HIV-positive patients do not in general trigger overt increases in procalcitonin synthesis,[21,23] provided that the infections are localised or organ-related without systemic inflammation.

Neopterin levels were increased above normal (10 nmol/l) in 92% of the ART-naïve group and in 75% of the ART group. The levels were significantly higher ($p<0.01$) in the ART-naïve group and were inversely associated with CD4 counts. These results confirm the value of neopterin levels as a reflection of the degree of immunodeficiency. Fig. 1 shows the increase in CD4 counts that occurred over the same periods on ART as the decrease in neopterin. This implication (that neopterin may be an indicator of the efficacy of ART) warrants further investigation.

Among the 18 patients (>26% of the study population; 50% on ART) in whom active TB-co-infection was confirmed at the baseline investigations, neopterin levels were significantly higher ($p<0.001$), and CD4 counts significantly lower ($p=0.028$), than among the patients without TB co-infection. These results are in agreement with previous indications that neopterin levels are significantly higher in HIV-positive patients with TB-co-infections and that, although neopterin levels may decrease with anti-TB therapy, high levels of neopterin persist with progression of the immune deficiency and a poor prognosis.[24]

As neopterin levels reflect the degree of immune deficiency in HIV-positive patients, and perhaps the response to ART, the question was asked whether neopterin has indeed, as claimed elsewhere, prognostic value concerning disease progression.[25] Baseline neopterin was significantly higher ($p<0.01$) in the group of patients in whom other complications were present 6 months after baseline investigations, than patients who progressed well (53.9±39.9 v. 10.8±7.6 nmol/l; $p<0.01$). When all patients who stopped ART over the 6-month period were excluded, the mean neopterin levels were significantly higher in the group with complications than in the group without complications (59.29 v. 30.9 nmol/l; $p=0.018$). When those patients who did not change antiretroviral status were split into groups, the mean neopterin levels were significantly higher in the group that developed complications than those who did not, both for the ART (45.9 v. 24.13 nmol/l; $p=0.04$) and the ART-naïve (75.02 v. 30.99 nmol/l; $p=0.001$) groups. Although these results do not necessarily imply a direct relationship, they warrant further investigation. The possibility that neopterin levels could perhaps be predictive of disease progression was further examined by looking at the changes in CD4 counts. The baseline neopterin values were compared between patients whose CD4 counts decreased and those that increased over the 6-month period following baseline assessments. To minimise the number of confounding factors, any patient who had additional complications or a change in ART during the 6 months was excluded. This resulted in a drastic decline in sample sizes, i.e. 11 patients (8 on ART) had a

decrease, and 9 (all on ART) had an increase in CD4 counts over the period. Mean baseline neopterin levels were significantly higher in patients whose CD4 counts decreased, and significantly lower in patients whose CD4 counts increased. In the group whose CD4 count decreased over the 6-month period, baseline neopterin levels correlated with both baseline CD4 counts (r=-0.68; p=0.03) and follow-up CD4 counts (r=-0.58; p=0.07). Although the group divisions, owing to the exclusion criteria, were small, the association of neopterin levels with CD4 counts is nonetheless seen. These results warrant further investigation into the value of neopterin as a possible predictor of disease progression.

In view of the stimulatory role of IFN-γ in neopterin synthesis,[11] the link between chronic elevation of IFN-γ and HIV-1 progression, as well as the active role of neopterin in the disease,[25] the value of neopterin is not surprising. Neopterin has previously been described as one of the better immunological markers in patients with HIV-1 infections.[14,25] It has even been said that neopterin levels increase before other markers of HIV infections have risen.[25] In the present study, 40% of ART, and 75% of ART-naïve, patients had CD4 counts <200 cells/μl, and all had CD4 counts <400 cells/μl. Therefore, with regard to patients in the advanced stages of the disease, the results of this study support the notion of neopterin as an inexpensive indicator of CD4 status and as an indicator of bacterial co-infection. The results warrant further investigation into neopterin as an indicator of disease progression and of the success of ART.

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