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Neopterin and β2-Microglobulin as Prognostic Indices in Human Immunodeficiency Virus Type 1 Infection

Summary: The great majority of individuals with human immunodeficiency virus type 1 (HIV-1) infection presents with no signs or symptoms, or only lymphadenopathy. To initiate prophylactic measures in time it is necessary to establish risk criteria. CD4+ cell counts are significant predictors. Supplementary methods to improve the predictive information of CD4+ cell counts are still required. In addition, CD4+ cell counting is laborious, expensive, and restricted to specialized laboratories. Thus, there is also a place for more easily performed laboratory tests with similar predictive value as CD4+ cell counts. Neopterin and β2-microglobulin levels proved to be significant predictors of AIDS risk in HIV-1 seropositives. The predictive value of both parameters is equal to CD4+ cell counts and both markers are significant joint predictors in addition to CD4+ cell counts. Measurement of the parameters is done in serum (neopterin and β2-microglobulin) or urine (neopterin) specimens which reduces the risk of HIV-1 transmission compared to handling of whole-blood samples as it is required for cell counting. Although more studies are needed, especially in developing countries and in persons receiving zidovudine, it can be recommended to use neopterin and β2-microglobulin as additional marker to estimate AIDS risk in HIV-1 seropositive individuals. Moreover, both markers may be useful for this purpose without CD4+ cell counts if cell counting is not available.

Zusammenfassung: *Neopterin und β2-Mikroglobulin als Prognoseindices bei Infektionen mit dem humanen Immunschwächevirus Typ 1 (HIV-1).* Die Mehrheit der mit dem humanen Immundefizienzvirus Typ 1 (HIV-1) infizierten Personen ist frei von Symptomen oder weist nur persistierende Lymphadenopathie auf. Es ist notwendig, Risikokriterien für das Fortschreiten der Erkrankung zu erstellen, um zeitgerecht prophylaktische Maßnahmen einleiten zu können. Die Zahl der CD4-positiven Zellen ist ein geeigneter Prognoseparameter. Die Zellzählung ist jedoch aufwendig, teuer und Speziallabors vorbehalten, sodaß zusätzliche einfache Untersuchungen erwünscht sind, um die Risikoabschätzung weiter zu verbessern. Wissenschaftliche Untersuchungen ergaben, daß Neopterin und β2- Mikroglobulin bei der HIV-1 Infektion gleich gute Prognoseparameter sind wie die Zahl der CD4-positiven Zellen; beide Parameter liefern darüber hinaus zusätzliche Information. Die Bestimmung der Meßgrößen erfolgt aus Serum (Neopterin und β2-Mikroglobulin) oder Urin (Neopterin), wodurch das Risiko einer eventuellen HIV-1 Übertragung bei der Testdurchführung im Vergleich zur Bearbeitung von Vollblut, wie es zur Zellzählung benötigt wird, verringert wird. Auch wenn noch weitere Untersuchungen vor allem in Entwicklungsländern und in mit Zidovudin behandelten HIV-1 Infizierten notwendig sind, können Neopterin und β2-Mikroglobulin als zusätzliche Parameter zur Abschätzung des AIDS-Risikos bei HIV-1 Infizierten empfohlen werden. Beide Meßgrößen sind auch dazu geeignet, die Bestimmung von CD4- positiven Zellen zu ersetzen, wenn die Möglichkeiten der Zellquantifizierung nicht gegeben sind.

Introduction

Human immunodeficiency virus type 1 (HIV-1) is the causative agent for the acquired immunodeficiency syndrome (AIDS). Today the diagnosis of HIV-1 infection can routinely be performed with more than 95% diagnostic sensitivity and specificity of the available test systems. From the first epidemiologic surveys it became evident that the great majority of individuals who were diagnosed as HIV-1 seropositive presented with no signs or symptoms or only with lymphadenopathy. Follow-up studies performed in cohorts of homosexual men, haemophilia patients, and intravenous drug users (IVDU) showed an annual AIDS progression rate of HIV-1 seropositives between 5–10% [1]. To allow early initiation of prophylactic measures in HIV-1 seropositives, indicators of disease progression are required for monitoring of HIV-1 seropositive individuals. By this strategy, it is hoped to prevent or at least delay the onset of opportunistic infections in subjects at increased risk for AIDS.

Progressive HIV-1 infection is associated with a steady decline of CD4+ cell numbers [2], and a low number of CD4+ cells is a predictive marker of an increased risk for

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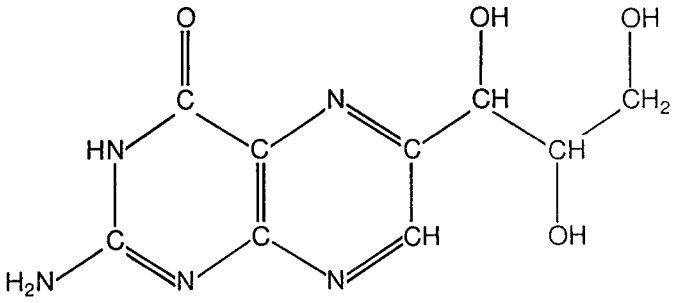

Figure 1: Neopterin (6-D-erythro-trihydroxypropylpterin).

disease progression in HIV-1 seropositives [3, 4]. However, counting of CD4+ cells is laborious, time-consuming and expensive. Therefore, it is important to develop supplementary or alternative methods which are more readily available to clinical laboratories and which are easily performed. Of course, such tests need to indicate an increased risk for AIDS among HIV-1 seropositives with similar sensitivity and specificity as CD4+ cell counting does.

Neopterin

Biosynthetically D-erythro-neopterin (Figure 1) derives from guanosinetriphosphate. *In vitro*, human macrophages produce and release large amounts of neopterin on stimulation with interferon gamma. Increased neopterin concentrations have been demonstrated in patients with diseases associated with or caused by cell-mediated immune activation [5, 6] as with allograft rejections, autoimmune disorders, infections by viruses, intracellular bacteria and parasites, and certain types of malignant tumours.
In general, neopterin concentrations reflect the extent and the activity of the disease. Therefore, neopterin is a useful marker to monitor therapy in patients. In patients with malignant tumours, a significant predictive value of neopterin was demonstrated by several investigators [reviewed in reference 5].
Measurement of neopterin in body fluids such as urine, serum, cerebrospinal fluid (CSF) is usually done by commercially available immunoassays or high pressure liquid chromatography (HPLC) techniques. Neopterin concentrations in spot urine samples are related to creatinine levels to account for physiological variations of urine density.

β2-Microglobulin

β2-Microglobulin (B2M) is a low molecular weight protein of 11,800 Dalton. It is the light chain of the major histocompatibility complex (MHC) class I antigens HLA-A, HLA-B, and HLA-C. MHC class I antigens are expressed on the surface of all normal nucleated cells, being present in highest density on lymphocytes. Shedding of B2M from cells is enhanced during proliferation and differentiation. Recently, it was shown that B2M possesses chemotactic activity for lymphoid cells and that it is identical with thymotaxin [7].

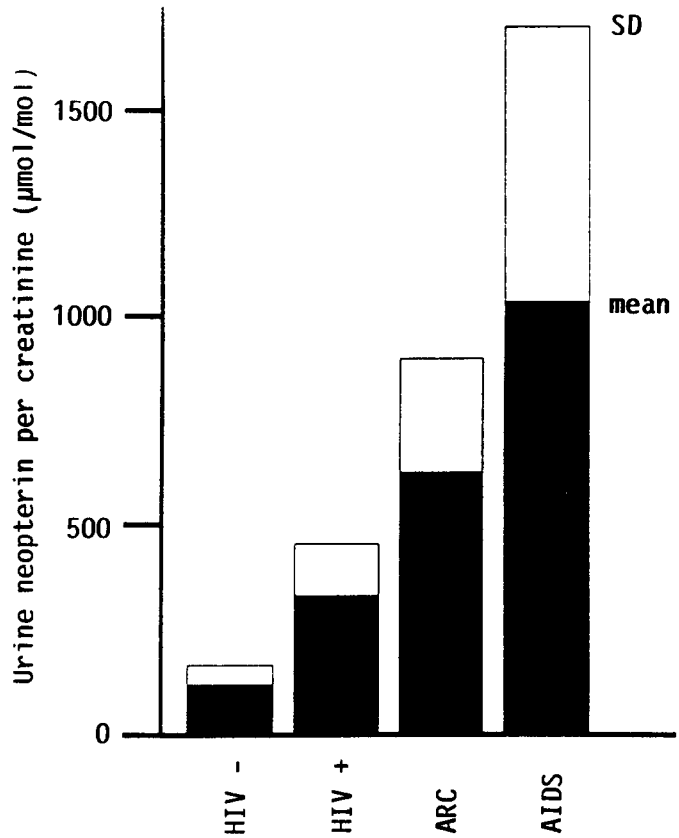

Figure 2: Urinary neopterin concentrations in individuals with different stages of HIV-1 infection.

Serum B2M levels are increased in diseases characterized by increased cell turnover, like malignancy [8] and chronic inflammation, e.g., rheumatic diseases and infections, but may be due also to renal impairment. Stimulation of immune cells, preferentially of lymphocytes [9] and macrophages, and the activity of specific cytokines such as interferon gamma [10] contribute to B2M increase via enhancement of MHC class I expression on target cells.
For diagnostic purposes, B2M levels in body fluids are usually quantified using commercially available immunoassays.

Evaluation of Neopterin in HIV-1 Infection

In 1983 increased neopterin concentrations were reported in urine of patients with AIDS and with generalized lymphadenopathy [11]. The increase of serum and urine neopterin concentrations parallels disease progression in HIV-1 seropositives, and a significant association between neopterin and various staging classification systems was found [6, 12, see Figure 2]. Asymptomatic HIV-1 seropositives have increased neopterin levels with high percentage compared to HIV-1 seronegative blood donors. Neopterin concentrations correlate negatively with CD4+ cell counts in HIV-1 seropositives [13], and neopterin levels were found to be at least equally sensitive and specific as CD4+ cell counts to discriminate between HIV-1 seropositive and seronegative homosexuals [13, 14]. As was shown in retrospective analyses of sequentially collected samples

Table 1: The time-dependent posterior probability for AIDS as a function of urinary neopterin levels (μmol neopterin per mol creatinine).

Urine neopterin	AIDS incidence 1, 2, 3, 4.5 years after initial neopterin measurement			
	1	2	3	4.5
200	1.64%	4.94%	9.51%	16.2%
400	3.89%	10.7 %	18.8 %	31.1%
800	19.3 %	39.0 %	54.9 %	71.3%
1200	58.5 %	77.3 %	86.5 %	93.2%

from HIV-1 seroconverters, a higher increase of serum neopterin concentrations after exposure to HIV-1 was associated with a more rapid subsequent fall of CD4+ cell counts [15].

Prospective and retrospective analyses showed that neopterin concentrations in urine [16, 17] and serum [15, 18–20] are significant predictors for the onset of AIDS in HIV-1 seropositives. Serum or urine measurements are of equal value [21], and it turned out according to all surveys that neopterin concentrations are of similar predictive significance as CD4+ cell counts. Moreover, neopterin concentrations and CD4+ cell counts are significant joint predictors for the onset of AIDS. Thus, measurement of neopterin to predict prognosis in HIV-1 seropositives provides information which is of similar significance as CD4+ cell counts and adds significant information when being used in addition to CD4+ cell counting.

However, grouped data only allow statistical analysis of the predictive potential of a laboratory parameter. For prospective monitoring of HIV-1 seropositive individuals it is necessary to use an individual AIDS-risk estimate composed of single or multiple laboratory parameters. *Bogner* et al. concluded from their data that serum neopterin levels above 22nmol/l may indicate the manifestation of AIDS in the year to come [18]. Table 1 shows the result of a calculation of AIDS risk based on urine neopterin data from reference 17. In contrast to CD4+ cell counts (not shown), neopterin levels provide an AIDS-risk estimate for several years (Table 1): The AIDS risk correlates with the height of urine neopterin levels and increases with time (*Reibnegger* et al., Clin. Chem., in press).

Evaluation of β2-Microglobulin in HIV-1 Infection

In 1983 increased serum B2M levels were reported in patients with AIDS [22]. Subsequently, B2M levels were described as increasing with the stage of HIV-1 infection [23, 24]. In contrast to neopterin results, B2M levels increase to abnormal levels preferentially in advanced stages of HIV-1 infection, whereas the great majority of asymptomatic HIV-1 seropositives presents with B2M levels below 2.5 mg/l, which is the 95th percentile of HIV-1 seronegative controls [19, 25]. The B2M mean value in AIDS patients is approximately four times the mean value of HIV-1 seronegative controls (Figure 3).

Retrospective analyses of HIV-1 seroconverters showed that the change of B2M after exposure to HIV-1 is associated with the decline of CD4+ cell counts during the following months [25].

Retrospective studies further demonstrated that serum B2M concentration is a significant predictor of AIDS in HIV-1 seropositives [19, 20, 25, 26]. In all surveys B2M levels turned out to be of similar value as CD4+cell counts for predicting the onset of AIDS in HIV-1 seropositive individuals. Moreover, B2M predicted disease progression independently from CD4+ cell counts. Both markers are significant joint predictors.

Neopterin and/or β2-Microglobulin to Predict the Onset of AIDS in HIV-1 Seropositive Individuals

Serum and urine neopterin and serum B2M levels behave similarly during the course of HIV-1 infection. The relative increase during HIV-1 infection compared to baseline levels of HIV-1 seronegative controls is higher for neopterin (10-fold increase, Figure 2) compared to B2M changes (Figure 3). Neopterin reaches earlier abnormal levels during the course of HIV-1 infection than B2M. However, correlation coefficients up to 0.8 were observed in studies comparing both markers (Figure 4).

Neopterin and B2M are of similar value as CD4+ cell counts to predict disease progression in prevalent HIV-1 seropositives. In a study of various serologic and immunologic markers to predict the onset of AIDS [19], relative-hazard characteristics were again similar for CD4+ cells (log- likelihood = –456.65), CD4+ percentage (–455.70),

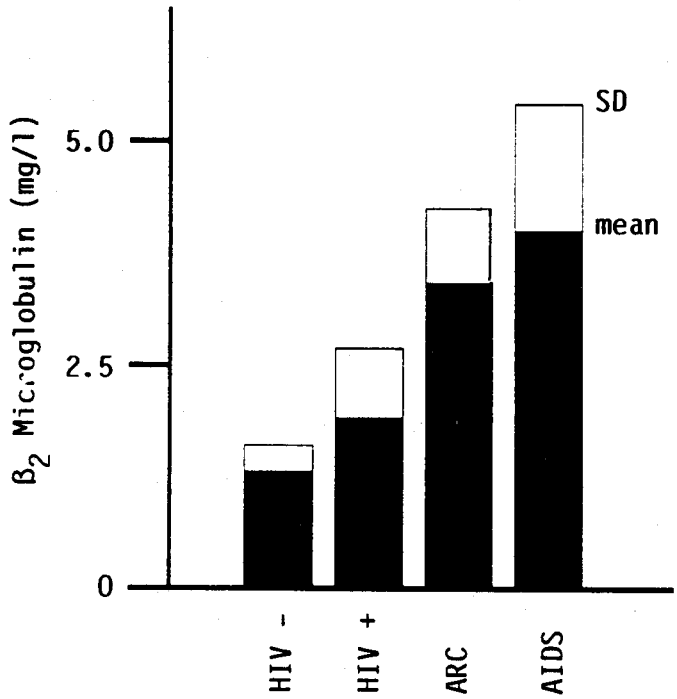

Figure 3: Serum β2-microglobulin concentrations in individuals with different stages of HIV-1 infection.

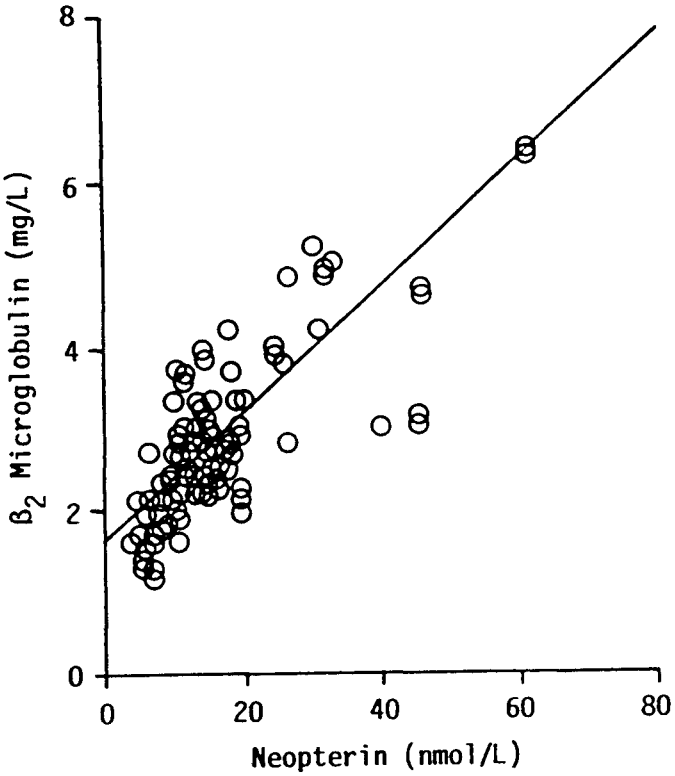

Figure 4: Correlation between serum neopterin and β2-microglobulin in 99 HIV-1 seropositive individuals (Spearman rank correlation coefficient $r_s = 0.744$, $P < .001$).

CD4+/CD8+ cell ratio (–454.21) and neopterin (–457.74), when the parameters were applied as single predictors (the less negative the log-likelihood, the more significant is the corresponding variable). B2M (–464.35), soluble interleukin-2 receptor (sIL-2r; –465.98), and IgA (–464.20) had weaker potential to predict AIDS.

In combination with CD4+ cell counts, neopterin or B2M were of identical value (log-likelihood = –448.17 and –449.45, respectively). In this study, the best combination of markers to model the risk of AIDS consisted of CD4+ cells, neopterin, sIL-2r, IgA and (presence or absence of) p24 antigen (– 432.31).

Retrospective time-dependent analyses in a cohort of homosexual men [20] showed that the CD4+ cell percentage significantly predicted AIDS onset 48–60 months before diagnosis ($p = 0.008$). Serum neopterin ($p < 0.001$) and B2M ($p = 0.02$) became significant 24–36 months before onset of AIDS; 2–12 months before the diagnosis of AIDS, B2M was the best single predictor ($p < 0.001$). In agreement with this, a prospective study showed a significant predictive value during six years for urine neopterin concentrations [17].

Conclusions

Neopterin and B2M are useful laboratory parameters to define AIDS risk in HIV-1-seropositive individuals. Both parameters reflect immune activation in patients, and therefore, changes of neopterin and B2M are not specific for HIV-1 infection. Although variation of CD4+ cell counts can be considered a significant aspect of HIV-1 pathology, the predictive value of neopterin and B2M equals that of CD4+ cell counts. Therefore, and because they are significant predictors jointly with CD4+ cell number, neopterin and/or B2M can be recommended as additional markers to improve the estimation of AIDS risk in HIV-1 seropositives even when CD4+ cell counts are available. Moreover, neopterin and B2M are likely to be of considerable value if CD4+ cell counting is not available, although the predictive value of these assays in developing nations, and to a lesser extent in IVDUs, remains to be proven. In addition, these markers may be valuable for monitoring therapy with zidovudine [27–29].

In combination with CD4+ cell counts, neopterin and B2M are of similar value to estimate prognosis. When used as single parameters, neopterin appears to be slightly more sensitive to indicate immunological alterations in HIV-1 seropositive compared to HIV-1 seronegative individuals during the early course of infection [19, 20]. However, in prospective follow-up of HIV-1 seroconverters both markers, neopterin and B2M, were significantly predictive for the onset of AIDS even one year after seroconversion [30]. Additional studies are required to further clarify this point.

The possibility to establish more accurate risk criteria in HIV-1 seropositive individuals may help to optimize prophylactic measures in patients and to select even asymptomatic patients, who are at greater risk for AIDS, for antiretroviral treatment.

Measurement of neopterin and B2M is feasible using only a few microliters of serum. Immunoassays can be performed outside of specialized laboratories, and samples can be posted from the periphery to the laboratory for measurement. Handling and pipetting of serum samples is less infectious than of whole blood, and the risk of HIV-1 transmission is close to zero when using urine samples for neopterin measurements.

Importantly, neopterin concentrations correlate significantly with virus isolation frequency in patients and with reverse transcriptase activity of HIV-1 isolates [31]. Moreover, neopterin values correlate significantly and positively with circulating interferon gamma levels in HIV-1 seropositives [32]. The significance of neopterin and B2M to monitor and even to predict the course of HIV-1 infection underlines the relevance of immune activation for the pathogenesis of the disease [6]. In patients, immune activation may upregulate HIV-1 reproduction in infected cells. It is necessary to recognize that chronic activation is ongoing at a high level in HIV-1 seropositives. The higher the degree of activation, even in asymptomatic individuals, the more rapidly disease progression will develop.

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