Expanding Role of Circulating Adhesion Molecules in Assessing Prognosis and Treatment Response in Human Immunodeficiency Virus Infection

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To patrol the body effectively and to generate an immune response to infectious organisms, the effector cells of the immune system must be able to congregate in lymphoid organs, to migrate to inflammatory tissues by crossing endothelial and basement membrane barriers, and to adhere to cells bearing foreign antigens. These actions are mediated by a number of surface accessory molecules, the adhesion molecules, which bind to specific counter-receptors expressed on endothelial cells, other cells of the immune system, and/or extracellular matrix components (60, 82). Moreover, adhesion molecules transduce activating signals for T-helper, T-cytotoxic, and B cells (42) and are involved in their differentiation, proliferation, antigen recognition, migration and trafficking, cytokine production, and apoptosis (13, 76, 82). Adhesion molecules are classified into three families: the selectins, the integrins, and the immunoglobulin superfamily (60, 82). Expression of adhesion molecules on the surfaces of immune cells is widely induced by cytokines released during immune activation; therefore, aberrant expression has been described in various diseases characterized by immune activation, including autoimmune, malignant, and infectious diseases (29, 74).

Proteolytic cleavage of several membrane-bound adhesion molecules results in the release of soluble isoforms into circulation. Although there is some evidence that circulating adhesion molecules (CAMs) interfere with various cell-cell interactions and may act as signal transducers, their possible biological role still remains unclear. Circulating adhesion molecules have been found in the sera of healthy individuals, and increased levels have been described in various immune-mediated diseases (29).

Numerous studies, summarized in Table 1, have shown that human immunodeficiency virus (HIV) infection is associated with abnormalities in the synthesis and expression of various adhesion molecules. Consequently, abnormal levels of circulating isoforms have been reported in HIV-infected patients (29, 52). Although numerical and functional decline of CD4 T cells is a major feature, the immunodeficiency associated with HIV infection is a much more complex process involving several pathogenic mechanisms mediated by adhesion molecules, such as altered function, distribution, and migration of lymphocytes and dysfunction of neutrophils (58).

The aim of this review is to summarize the available data on the aberrations of the levels of certain CAMs in HIV-infected patients, as well as on their biological significance, their prognostic value regarding the course of the disease, and their potential role in assessing the efficacy of highly active antiretroviral treatment (HAART).

CIRCULATING ADHESION AND LYMPHOID COSTIMULATORY MOLECULES IN HIV INFECTION

HIV infection leads to a compensatory, chronic immune activation (14), resulting in altered expression of cell surface antigens and in increased production of cytokines. Cytokines, in turn, along with other factors such as concurrent opportunistic infections and immune reconstitution, up-regulate the expression of adhesion molecules on the surfaces of immune and endothelial cells, and subsequently the levels of circulating adhesion molecules are increased. A recent study showed that elevated levels of CAMs may reflect the activation of the non-adaptive immune response to HIV. More specifically, the virus per se was found to be responsible for increased oxidative stress that subsequently activates various transduction pathways and thus leads to endothelial-cell activation and shedding of adhesion molecules from the cell surface (84).

The alterations in the expression of adhesion molecules may lead to abnormalities in the interactions of neutrophils, lymphocytes, and endothelial cells, contributing to the general dysfunction of the immune system observed during the course of HIV infection (32). In addition, increased expression of adhesion molecules may facilitate the extravasation of HIV-infected cells, thus contributing to the establishment of viral reservoirs in tissues and to specific tissue damage associated with various HIV-associated syndromes, such as HIV dementia and HIV nephropathy (87).

The biological significance of the increased levels of circulating isoforms of adhesion molecules in HIV infection is less clear. There are two ways in which CAMs may exert a physiological role: by competing in cell-cell adhesion and/or by triggering a response in a ligand-bearing cell. There are several lines of evidence suggesting that elevated levels of CAMs may lead to defective cell-cell interactions, including adherence of phagocytes to endothelial cells, chemotaxis, and diapedesis (29).

SOLUBLE SELECTINS IN HIV INFECTION

The selectin family of adhesion molecules comprises three members: L-, P-, and E-selectin. Selectins interact with carbohydrate ligands and mediate the initial rolling of leukocytes on
the endothelium (4). Soluble forms exist for all three selectins, and their levels are elevated in patients with HIV infection.

L-selectin (CD62L) is expressed on the surfaces of granulocytes, lymphocytes, and monocytes and is responsible for the initial attachment of leukocytes to the endothelium. The expression of L-selectin on various cells is reduced during HIV infection (Table 1). The extracellular domain of L-selectin is proteolytically cleaved from leukocytes following cellular activation in vitro. The soluble form of L-selectin (sLs) is functionally active and at high concentrations can inhibit leukocyte attachment to the endothelium (72). Initial studies of patients with HIV infection showed a two- to threefold increase in sLs levels compared to those in healthy controls (81). For some patients with AIDS, sLs levels were above those required to completely inhibit leukocyte attachment to the endothelium in vitro (81). In a more recent study, levels of sLs in treatment-naive HIV-infected patients were twofold higher than those in seronegative controls (45). The finding that in HIV infection the levels of sLs are increased despite the HIV-driven down-regulation of the expression of L-selectin on the surfaces of leukocytes (32, 47, 59, 63) might seem paradoxical. A possible explanation is that down-regulation of the surface L-selectin molecule might be associated with increased cleavage and/or decreased clearance, thus resulting in elevated serum sLs levels. As has recently been shown, engagement of both the CD4 molecule and the HIV coreceptor CXCR4 is required for HIV-induced L-selectin shedding on CD4-expressing T lymphocytes (86).

P-selectin is stored in platelets and endothelial cells and is expressed on the cell surface upon activation (4). Soluble P-selectin (sPs) has been shown to inhibit the adhesion of neutrophils via CD11b to the endothelium, thus exerting an anti-inflammatory action (27). Increased levels of sPs have been found in 84 HIV-infected patients compared to 84 healthy controls (8), a finding confirmed in another recent study (89). The increased sPs levels were not correlated with the stage of the disease and were possibly related to platelet activation due to the HIV infection (7). High levels of sPs, along with high levels of von Willebrand factor, may contribute to the well-known increased risk of thrombosis observed in HIV-infected patients (6).

E-selectin (CD62E), in contrast to other adhesion molecules, is expressed only on activated endothelium, and it mediates the adhesion of various immune cells to vascular endothelium (43). HIV, through its Tat protein (20, 35), induces the expression of E-selectin on human endothelial cells, thus promoting the extravasation of HIV-infected cells (Table 1). Soluble E-selectin (sEs) is released from the endothelial cells following activation (51). sEs is biologically active; it can inhibit leukocyte adhesion (29) and activate polymorphonuclear cells via the CD11b integrin receptor (44). As we have shown, levels of sEs in HIV-infected patients (without concomitant fever, opportunistic infection, or neoplasm) are elevated compared to those in healthy controls, while a significant increase was observed with disease progression (75). Although some subsequent studies confirmed the elevated levels of sEs compared to those for healthy controls (52, 73), in other studies no significant differences were demonstrated (3, 28, 45) (Table 2). This was probably due to the fact that these studies included patients with concomitant opportunistic infections or neoplasms. Interestingly, the presence of Kaposi's sarcoma or cytomegalovirus infection results in a decrease in serum sEs levels, probably through down-regulation of the expression of E-selectin on endothelial cells (3, 45).

### Soluble Immunoglobulin Superfamily Adhesion Molecules

Immunoglobulin superfamily molecules contain extracellular immunoglobulin domains and mediate intercellular adhesion. Expression of these molecules on the cell surface is up-regulated during the immune response, mediating cell activation and migration (29). Elevated levels of the soluble forms of three immunoglobulin superfamily adhesion molecules, intercellular adhesion molecule-1 (ICAM-1, or CD54), vascular cellular adhesion molecule-1 (VCAM-1, or CD106), and the CD40 ligand (CD40L, or CD154), have been reported in patients with HIV infection (52, 77, 79) (Table 2).

ICAM-1 is expressed in significant amounts on monocytes and endothelial cells, but it is also widely inducible by proinflammatory cytokines on many other cell types (70). Besides its role in cell-cell interactions, ICAM-1 has an important costimulatory effect on T-cell activation (85). During the course of HIV infection, ICAM-1 plays an important pathogenetic role (10, 34) and its expression on immune cells is increased (Table 1). A circulating form of ICAM-1, which is probably cleaved from the surfaces of ICAM-1-bearing cells, has been detected in culture supernatants and human body fluids (69). This soluble ICAM-1 (sICAM-1) is functionally active in vitro (31, 69), but its in vivo role remains unknown (29). A recent study showed that macrophages that express the HIV protein Nef or are activated through the CD40 receptor release soluble CD23 and sICAM-1, which render T lymphocytes permissive to infection (83). Numerous studies have reported increased serum sICAM-1 levels in adult and pediatric patients with HIV infection (Table 2). A further increase has been observed in patients with concomitant opportunistic infections (52), Kaposi's sarcoma (3, 19), or neurological disease (33). Levels of

### Table 1. Effects of HIV infection on the expression of certain adhesion molecules

| Molecule | Expression on the surfaces of various cells during HIV infection | References |
|----------|---------------------------------------------------------------|------------|
| L-selectin (CD62L) | CD8+ T cells, CD4+ T cells, monocytes, neutrophils | 32, 47, 59, 63 |
| E-selectin (CD62E) | Endothelial cells | 20, 35, 53, 66, 90, 92 |
| ICAM-1 (CD54) | Lymphocytes, endothelial cells | 9, 20, 36, 59, 66, 67, 90 |
| VCAM-1 (CD106) | Endothelial cells | 20, 53, 71, 92 |
| CD40 ligand (CD154) | CD4+ T cells | 12, 37, 38, 49, 80 |
| CD91 (DEC-205) | Activated T cells | 30, 31 |

**References**

1. Vol. 11, 2004 MINIREVIEWS 997
2. Table 1. Effects of HIV infection on the expression of certain adhesion molecules.
sICAM-1 in cerebrospinal fluid (CSF) were elevated only in HIV-positive patients with neurological disease (33), mainly due to passive diffusion through a defective blood-brain barrier (68). Increased levels of sICAM-1 were also observed in the bronchoalveolar lavage fluids of HIV-infected patients (9).

The related molecules ICAM-2 (CD102) and ICAM-3 (CD50) are implicated in synctium formation and the subsequent cell-to-cell transmission of HIV (10). Elevated levels of the soluble isoforms of both molecules have been reported in patients with HIV infection (26, 45).

VCAM-1 is an adhesion molecule expressed mainly on endothelial cells (55), and its expression is induced by HIV (Table 1). It mediates the adhesion of immune cells to activated vascular endothelium and their subsequent migration, but it also serves as a costimulatory molecule in T cells (15). A soluble form of VCAM-1 (sVCAM-1) has been identified (61), also serves as a costimulatory molecule in T cells (15). A soluble form of VCAM-1 (sVCAM-1) has been identified (61), and its expression is induced by HIV (Table 2).

TABLE 2. Changes in levels of CAMs in HIV-infected patients

| CAM                      | Levels of CAM in HIV infection (refs)* | Correlation with clinical stage (refs) | Correlation with CD4+ T-cell count (refs) | Effect of HAART on CAM levels (refs) |
|--------------------------|----------------------------------------|---------------------------------------|------------------------------------------|-------------------------------------|
| Selectins                |                                        |                                       |                                          |                                     |
| sLs                      | Increased (45, 81)                     | None (8)                              | None (45)                                | Decreased (45)                      |
| sPs                      | Increased (6, 8, 89)                   | Positive (75)                         | Positive (52)                            | No effect (89)                      |
| sEs                      | Increased (52, 73, 75)                 | None (52)                             | None (45, 75)                            | No effect (45)                      |
| Immunoglobulin superfamily |                                       |                                       |                                          |                                     |
| sICAM-1                  | Increased (1, 3, 19, 21, 25, 26, 28, 33, 45, 50, 52, 54, 64, 65, 77, 89, 91) | Positive (1, 25, 26, 28, 33, 52, 64, 77) | Inverse (25, 64, 78)                  | No effect (45)                      |
| sICAM-2 and sICAM-3      | Increased (26, 45)                     | None (50, 54)                         | None (21, 28, 33, 45, 50, 52, 91)        | Decreased (89)                      |
| sVCAM-1                  | Increased (3, 17, 26, 28, 45, 52, 89)  | Positive (52)                         | Inverse (52)                             | Decreased (45)                      |
| sCD40L                   | Increased (79, 89)                     | None (20)                             | None (28, 45)                            | Decreased (17, 45, 89)             |

* refs, references.

Given the time from initial infection to the development of clinical AIDS varies greatly, there is a need for laboratory markers to monitor the course of HIV infection prior to the onset of clinical signs and symptoms. These markers depict the damage to the immune system caused by HIV, provide information on the pathogenesis of the disease, and guide treatment decisions (24).

The prognostic significance of soluble adhesion molecules has been assessed in numerous studies. These studies were motivated by the need for new, easily measured prognostic markers in HIV infection, since the existing markers either are expensive, requiring sophisticated laboratories (CD4+/CD8+ T-cell counts and viral load), or have low predictive value (immune activation markers).

Elevated serum sICAM-1 levels represented the marker most extensively studied for prognostic value. In the majority of the published studies, increased circulating levels of sICAM-1 correlated with advanced disease (Table 2). For instance, in one study performed in our laboratory, a highly significant correlation between elevated serum sICAM-1 levels and clinical disease progression from category A to clinical categories B and C was observed, while AIDS patients had significantly higher levels than HIV-infected non-AIDS patients (77). Similar results were observed in the majority of studies which investigated the correlation of sICAM-1 levels with clinical progression (Table 2), with the exception of two studies of adult and pediatric patients (50, 54).

A strong indication that a soluble molecule might serve as a surrogate marker for disease progression is the degree of cor-

mokine production by macrophages and resistance to HIV entry (22, 40). Furthermore, the impaired interleukin-12 (IL-12) production observed in HIV-infected patients (11) could be due to the recently reported ability of sCD40L to inhibit IL-12 production (88).

PROGNOSTIC VALUE OF CAMS IN HIV INFECTION

Given the time from initial infection to the development of clinical AIDS varies greatly, there is a need for laboratory markers to monitor the course of HIV infection prior to the onset of clinical signs and symptoms. These markers depict the damage to the immune system caused by HIV, provide information on the pathogenesis of the disease, and guide treatment decisions (24). Levels of soluble markers of immune activation in serum, CD4+ T-cell counts, and viral load represent the three categories of markers which have been shown to predict disease progression (23, 46, 56, 62).

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A strong indication that a soluble molecule might serve as a surrogate marker for disease progression is the degree of cor-
relation with the existing markers. The data regarding the correlation of sICAM-1 levels with the main surrogate marker, the CD4+ T-cell count, are rather contradictory. The majority of the published studies did not find a significant correlation of serum sICAM-1 levels with CD4+ T-cell counts (Table 2), while three studies (25, 64, 77) reported a significant inverse correlation. Interestingly, in the only study of its kind, an inverse correlation between CSF sICAM-1 levels and CD4+ T-cell counts was reported (33). In two recent studies, sICAM-1 levels did not correlate with viral load, but this finding still needs to be confirmed (45, 89). Regarding the correlation of levels of immune activation markers in serum with confirmed prognostic value, a significant positive correlation was reported for β2-microglobulin (21, 25, 26, 91), serum and urinary neopterin levels (33, 50, 52), and soluble interleukin-2 receptors (77).

Validation of laboratory markers as surrogate markers of disease progression requires longitudinal studies. Along this line, we have measured serum sICAM-1 concentrations in a cohort of 64 HIV-infected patients between 1990 and 1993 (78). The patients were followed up prospectively for a median time of 46 months. Univariate analysis showed that baseline levels of sICAM-1 above the median value were a significant prognostic factor for time to death (relative hazard, 2.78; P = 0.005). However, this prognostic significance disappeared after adjustment for CD4+ T-cell counts, a finding that could be explained by the fact that the levels of this marker were inversely correlated with baseline CD4+ T-cell counts (78).

sVCAM-1 was also validated as a candidate surrogate marker (Table 2). A strong inverse correlation with CD4+ T-cell counts and a positive correlation with serum neopterin levels were reported in an early study (52). These results were not confirmed in two other studies (28, 45). Moreover, it has been shown that the levels of sVCAM-1 correlate with viral load (45, 89).

Regarding sEs, in the first published study, a significant increase with the clinical category disease progression was observed, while AIDS patients had significantly higher levels than HIV-infected patients without AIDS. Individual serum sEs levels correlated strongly with levels of sICAM-1 and IL-2 receptor in serum but not with CD4+ T-cell counts (75). Subsequent studies reported a marginal correlation or no correlation of sEs with CD4+ T-cell counts (45, 52). In a longitudinal study, baseline sEs levels had no predictive value for progression to AIDS or survival (78). The recently described elevated serum sCD40L levels correlated weakly with CD4+ T-cell counts but not with viral load (79). In contrast, in one study, sEs levels did not correlate with CD4+ T-cell counts but did correlate significantly with HIV RNA levels (45).

**EFFECTS OF HAART ON SERUM CAM LEVELS**

The introduction of HAART reduced the morbidity and mortality of HIV infection dramatically (57), thus making clinical events too rare to be considered primary end points for trials assessing the efficacy of various regimens. Therefore, most of the new antiretroviral drugs and/or combinations have been approved based on their effects on surrogate markers, i.e., CD4+ T-cell counts and virus load (18). In order to investigate the potential use of CAMs as easily determined markers of the efficacy of HAART, many studies have investigated the effects of antiretroviral treatment on serum CAM levels.

Studies performed prior to the advent of HAART showed that antiretroviral treatment with zidovudine had no effect on the elevated levels of sICAM-1 or sEs (75, 77). In contrast, a study of pediatric patients showed a statistically significant reduction in sICAM-1 levels in HIV-infected children undergoing therapy with zidovudine (54). HAART decreases (but does not normalize) the immune activation status and the levels of cytokines in HIV-infected patients (2, 5), thus leading to at least a partial reversal of abnormalities in adhesion molecule expression (48, 80). Recently, the effects of HAART on levels of sEs, sLs, sICAM-1, and sVCAM-1 in plasma were evaluated for 22 HIV-infected patients who were started on a HAART regimen and followed up for 9 months (45). The initially elevated levels of sLS were reduced to normal ranges after treatment. This finding is in accordance with other data showing that the decreased L-selectin expression on circulating polymorphonuclear lymphocytes before HAART increased to normal following the introduction of HAART (48). Serum sICAM-1 and sEs levels did not change after HAART, while the levels of sVCAM-1 and sICAM-3 decreased significantly but still remained higher than those of normal controls. In another study, 41 infected patients were evaluated before HAART and after 5 to 13 months of treatment. The initially high levels of sICAM-1 and sVCAM-1 were decreased (but not normalized), while sPs and sCD40L levels were not affected by HAART (89). Serum sCD40L concentrations were determined for a cohort of 77 HIV-infected patients before and after initiation of HAART in a study performed in our laboratory. In contrast to the findings of the study just mentioned, after 8 to 12 months of HAART, a further threefold increase in the already elevated serum sCD40L levels, paralleling the increase in CD4+ T cell counts, was observed (79). Finally, two studies comparing patients receiving HAART to patients not receiving HAART reported elevated sPs levels and decreased sVCAM levels in patients on HAART, while no difference was observed for sICAM-1 (16, 17).

**CONCLUSIONS**

HIV infection has a profound impact on the expression of adhesion molecules on the surfaces of immune and other cells, resulting in abnormal levels of soluble adhesion molecules in serum. The study of these molecules could provide additional information on their biological significance, which remains largely unknown, and on the pathogenesis of HIV infection. Of specific interest is their potential to serve as surrogate markers for disease progression and assessment of the efficacy of treatment, especially in resource-deprived settings, where equipment for measurement of the existing markers (i.e., CD4+ T-cell counts and virus load) is unavailable. The ideal serologic marker should be easy to measure and should have a low cost, a high predictive value, and the ability to identify confections, which are very common among HIV patients, especially in the Third World. Although the existing data are rather contradictory and inconclusive, possibly because of small patient numbers and selection bias, they point out that several soluble adhesion molecules have the potential to serve as surrogate markers. Therefore, large, well-designed prospective studies are needed.
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