Cytomegalovirus infection in the era of HAART: fewer reactivations and more immunity

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The incidence of cytomegalovirus (CMV) disease, once the most common and highly feared viral complication of AIDS, has dramatically decreased with the advent of highly active antiretroviral therapy (HAART). HAART-associated changes in the epidemiology of CMV disease resulted from the increase in CMV-specific immune responses coupled with the decrease in CMV reactivation. However, CMV disease continues to afflict HIV-infected patients on HAART when CD4+ cell counts fail to rise above 100 cells/mm³ and when reconstitution of normal CMV-specific immune responses does not occur. The latter scenario may lead to recurrent or de novo CMV end-organ disease, or to the recently described CMV immune recovery vitritis. HAART-associated immune reconstitution offers unique opportunities to investigate the virological and immunological correlates of protection against CMV disease. Although the full extent of CMV-specific immune reconstitution has not been defined thus far, CMV-specific interferon-γ production has been shown to be significantly associated with protection against CMV reactivation and recurrent disease.

Keywords: HIV, immune reconstitution, AIDS, opportunistic infections

Introduction

Cytomegalovirus (CMV) is a ubiquitous herpesvirus that generally causes asymptomatic or mildly symptomatic infection in immunocompetent hosts. In contrast, CMV infection in immunocompromised patients carries high morbidity and mortality. Before the introduction of highly active antiretroviral therapy (HAART), acquired immunodeficiency syndrome (AIDS) patients constituted the largest group severely affected by CMV, with a 10% annual incidence of sight- or life-threatening disease.1,2 The introduction of HAART in 1995–1996 caused a significant reduction in the incidence of AIDS-associated opportunistic infections including CMV.3 At the same time, new manifestations of opportunistic infections were identified and classified as immune recovery syndromes. We compare the clinical spectrum of CMV before and after HAART, while focusing on immune reconstitution.

CMV infection in patients with HIV before the introduction of HAART

Overview of clinical and epidemiological characteristics

CMV disease typically occurs when latent virus reactivates in AIDS patients with <100 CD4+ T cells/mm³. CMV infection in patients with <100 CD4+ cells/mm³ can be asymptomatic, or can cause non-specific symptoms such as fever and malaise or localized end-organ disease.4 The most common manifestation of CMV in HIV-infected individuals was retinitis, which occurred in 40% of AIDS patients and represented 85% of all CMV end-organ diseases.1 Gastrointestinal tract manifestations accounted for 10% of CMV disease in AIDS patients and the remainder consisted of neurological disorders, pneumonitis, hepatitis and adrenalitis.

Antiviral therapy against CMV relies on several effective drugs, such as ganciclovir, foscarnet and cidofovir. Due to intense immunosuppression and frequent viral reactivations, CMV disease tended to have a relentlessly progressive course1 and, therefore, patients with sight- or life-threatening manifestations were typically maintained on low-dose antiviral therapy indefinitely.5 However, the virus frequently developed resistance to the antivirals, causing relapse of clinical symptoms.5,8

Both symptomatic and asymptomatic CMV infections were associated with increased risk of death in AIDS patients.9 This might be due to organ failure related to CMV end-organ disease; because CMV active infection might be a marker of extremely severe immunosuppression, which ultimately leads to the fatal outcome of the patient; or because CMV infection might have down-regulatory effects on the immune system and thus predispose to death.

Viral reactivations

The factors that trigger CMV reactivation in AIDS patients are incompletely understood. At least one mechanism is tumour
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Table 1. Immunological and virological factors associated with protection against CMV disease in HIV-infected patients on HAART

<table>
<thead>
<tr>
<th>Non-specific markers</th>
<th>CMV-specific markers</th>
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<tbody>
<tr>
<td>CD4+ T cell count &gt; 100 cells/mm³</td>
<td>qualitative interferon-γ production in bulk mononuclear cell culture</td>
</tr>
<tr>
<td>HIV load &lt; 10 000 RNA copies/mL</td>
<td>circulating CD4+ interferon-γ-producing cells</td>
</tr>
<tr>
<td></td>
<td>circulating CD8+ interferon-γ-producing cells</td>
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<tr>
<td></td>
<td>absence of CMV DNA in blood</td>
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Current guidelines recommend discontinuation of secondary prophylaxis in HAART recipients with a sustained (≥6 months) increase in CD4+ T cells to levels of >100–150 cells/mm³. However, there are several reports of CMV retinitis occurring or progressing in patients taking HAART in the presence of CD4+ T cell counts of >100 cells/mm³.

A new clinical entity, CMV immune recovery vitritis, has been described in HAART recipients. This disease is characterized by posterior chamber inflammation, macular and disc oedema, neovascularization, cataracts and epiretinal membrane formation. Loss of visual acuity is common. It occurs in 15–90% of patients with previous CMV retinitis who experience increases in the number of CD4+ cells on HAART. The immunopathogenesis of this new disease is discussed below. There are conflicting data on the response to CMV antiviral treatment, but topical corticosteroids seem to improve symptoms.

Viral reactivations

HAART decreases the incidence of viraemia. In one study of 16 patients, HAART resulted in the disappearance of CMV DNA from circulation as detected by PCR without specific antiviral therapy. One potential mechanism is that control of HIV replication and opportunistic infections eliminates factors that would otherwise increase CMV reactivation, such as transactivation in cells co-infected with CMV and other pathogens or increased circulating TNF-α. In addition, we showed that CMV-specific interferon-γ production by in vitro-stimulated peripheral blood mononuclear cells was associated with a decreased risk of CMV reactivation in HAART recipients, arguing in favour of immunological control of CMV replication. The two mechanisms are not mutually exclusive and might jointly contribute to the decrease in CMV reactivation.

Immune responses

During the first 3 months of HAART both memory and naive circulating CD4+ cell counts increased. There is an initial increase, followed by a decrease in circulating CD8+ cells. Activation markers on circulating T cells and TNF-α serum levels decrease. Three to 6 months after HAART, patients reacquire delayed type hypersensitivity responses and in vitro lymphocyte proliferation assay (LPA) to microbial antigens. Both cellular and humoral CMV-specific immune reconstitution has been demonstrated in HAART recipients. CMV LPA responses increase with higher CD4+ cell counts and there is no significant

Immune responses

The integrity of the immune system is a decisive factor in the development of CMV end-organ disease. In CMV viraemic AIDS patients stratified by CD4+ counts of <50, 50–100 and >100 cells/mm³, the incidence of CMV end-organ disease over a period of 6 months was 25%, 5.5% and 1.3%, respectively. Not all individuals with AIDS and CMV reactivation progressed to end-organ disease and the factors that ultimately determined the development of symptoms are incompletely understood. CMV-seropositive AIDS patients who lacked lymphocyte proliferative responses to CMV had a higher risk of developing CMV end-organ disease, suggesting a protective role for cell-mediated immunity. In contrast, anti-CMV neutralizing and total antibody titres were comparable in AIDS patients to levels in healthy controls and in patients with less advanced HIV infection. Furthermore, administration of neutralizing anti-CMV monoclonal antibodies did not prevent or modify the course of the disease. These data argue against a protective role for CMV-specific humoral immunity. Many other immune parameters are altered in HIV-infected patients, but their contributions to the increased susceptibility of AIDS patients to CMV disease have not been adequately studied.

CMV infection in the era of HAART

Clinical and epidemiological features

HAART decreases HIV replication and increases CD4+ cell count. This is associated with a marked reduction in the incidence of opportunistic infections and increased survival. The incidence of new CMV retinitis has declined by ~80%, and survival in patients with CMV retinitis has increased by 93%. Risk factors for CMV end-organ disease in the HAART era continue to be CD4+ counts of <50–100 cells/mm³ and CMV reactivation (Table 1). In addition, an HIV viral load (VL) of >10 000 RNA copies/mL is associated with new CMV disease in HAART recipients.

necrosis factor (TNF)-α-mediated stimulation of the host cell, leading to nuclear factor κB (NF-κB) intranuclear accumulation and activation of CMV DNA replication. This might explain the high prevalence of CMV reactivation in conditions associated with increased synthesis of TNF-α, such as HIV infection.

CMV reactivations were most frequent in HIV-infected individuals with <100 CD4+ cells/mm³. When monitored systematically, 45–60% of these patients developed one or more episodes of circulating CMV DNA over a period of 6–12 months. Although CMV reactivations played a crucial role in the development of end-organ disease of AIDS patients, CMV replication was sometimes asymptomatic and self-limited. The positive predictive value of finding CMV DNA in plasma and white blood cells by PCR was ~60% and 40%, respectively. High titres of circulating CMV DNA increased the risk of end-organ disease.

Measures that prevented viraemia also decreased the incidence of the disease. Both oral and parenteral ganciclovir were successfully used for this purpose. However, the cost of prophylactic therapy for HIV-infected patients at risk of CMV disease before HAART was prohibitive.

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association between nadir CD4+ cells and CMV-specific immune reconstitution (A. Weinberg, unpublished results). However, immune restoration is incomplete, as illustrated by the inconsistency of CMV-specific CD4+-mediated proliferative responses,\textsuperscript{44,45} the dissociation between \textit{in vitro} mononuclear cell proliferation and cytokine production\textsuperscript{46} and the persistence of high levels of circulating CMV-specific CD8+ T lymphocytes.\textsuperscript{46} The mechanisms that account for incomplete immune reconstitution in HIV-infected patients are under investigation. There is evidence for both pathogen-specific and generalized immune defects. We described a HAART recipient with recurrent CMV retinitis despite an increase in circulating CD4+ T lymphocytes to >200 cells/mm\textsuperscript{3}. This patient was unable to mount \textit{in vitro} CMV-specific immune responses but had adequate \textit{Candida}-specific \textit{in vitro} responses,\textsuperscript{47} suggesting that CMV-specific clonal deletion or tolerance might have occurred. However, there is also evidence that HAART recipients who reconstitute immunity against a ubiquitous agent such as \textit{Candida} or CMV are more likely to reconstitute responses against other pathogens.\textsuperscript{48,49}

At the cellular level, several mechanisms have been implicated in the immune defect observed in HAART recipients. These patients have persistently high proportions of apoptotic circulating mononuclear cells despite control of HIV replication.\textsuperscript{50} There is a marked deficit of CMV-specific CD4+ T cell production of interleukin-2\textsuperscript{33,42,45,52} with downstream consequences on cell cycle progression\textsuperscript{53} and proliferation.\textsuperscript{52,54} Furthermore, there is evidence of down-regulatory activity mediated by CD4+ \textsuperscript{55} and CD8+ \textsuperscript{44} T cells.

The immune recovery vitritis or uveitis constitutes another example of altered immune responses in HIV-infected patients on HAART. This syndrome is characterized by exuberant retinal inflammatory infiltrates, which include CMV-specific cytotoxic T cells but also CD8+ T cells of broader specificity\textsuperscript{56} and seems to occur in the context of increased CMV-specific Th2 responses.\textsuperscript{57} In contrast, protection against CMV disease is conferred by Th1-specific cells. It is interesting to note that the eye, a segregated body compartment, but not the gastrointestinal or respiratory tract, is the main target of CMV-associated immune reactivation syndrome. It is tempting to speculate that the barrier between the eye chambers and circulation might impair the ability to establish normal immune regulatory processes in patients undergoing immune reconstitution.

Although it is well accepted that competent CMV-specific responses are critical determinants of CMV infection outcome, a user-friendly immunological test that can predict protection against CMV disease is not yet available. Immune reconstitution of HIV-infected patients on HAART has offered ample opportunity to examine immune correlates of protection against CMV disease. CMV-stimulated interferon-\gamma production measured in bulk culture supernatants\textsuperscript{13} or by flow cytometry in CD4+ \textsuperscript{58} or CD8+ \textsuperscript{59} cells has shown the best correlation with protection against CMV reactivation and disease (Table 1). Further work is needed, however, to establish the predictive value of CMV-specific interferon-\gamma assays in clinical practice.

References

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