Current Management of Cytomegalovirus Disease

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Cytomegalovirus (CMV) is an important pathogen for the fetus, for allograft recipients, and for acquired immunodeficiency syndrome (AIDS) patients; the clinical features in each of these groups of patients are described. CMV may also act as a cofactor to accelerate the rate at which the human immunodeficiency virus (HIV) causes AIDS. Active CMV infection in immunocompromised patients is best managed by routine laboratory screening of patients at risk using assays that provide prognostic information. Antiviral therapy can then be considered under one of four headings: For prophylaxis, the drug is given to all patients from a particular time point, e.g., time of transplantation. Successful trials have been reported for interferon (renal transplant), acyclovir (renal transplant and bone marrow transplant), and ganciclovir (heart transplant and bone marrow transplant). For suppression, the drug is given once CMV excretion has been detected in peripheral sites of particular patients. A successful trial of ganciclovir in bone marrow transplant patients has been reported. For preemptive therapy, the drug is given once CMV has been detected systemically. A successful trial of ganciclovir in bone marrow transplant patients has been reported. Regarding treatment, a controlled comparison of ganciclovir and foscarnet for CMV retinitis in AIDS patients has shown that both drugs are equally effective but that foscarnet has a survival benefit. Open studies suggest that the combination of immunoglobulin and ganciclovir is of benefit for treatment of established CMV pneumonitis. In open studies other treatments have been tried, with no clinical success, despite control of viral replication in some cases. It is suggested that this disparity is due to CMV pneumonitis being an immunopathological condition. This should emphasize that the basic biology of CMV must be understood if effective therapies are to be identified.

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INTRODUCTION

Cytomegalovirus (CMV) is important to four main groups of patients: the fetus, in whom it is the commonest agent causing intrauterine infection; recipients of solid organ transplants and bone marrow transplants, in whom it is the commonest infectious agent causing morbidity and mortality; acquired immunodeficiency syndrome (AIDS) patients, in whom it is second only to Pneumocystis carinii as an opportunistic infection, and to human immunodeficiency virus (HIV) asymptomatic individuals, in whom CMV may act as a cofactor to enhance progression to AIDS. Each of these groups of patients is discussed in this review.

Fetus

Intrauterine infection with CMV may present with symptoms of hepatosplenomegaly, jaundice, thrombocytopenia purpura, or microcephaly [Stagno, 1990]. This combination of symptoms and signs is termed cytomegalic inclusion disease and is found in ~7% of cases of intrauterine infection. Such children have a very poor prognosis, with a high fatality rate during infancy, and the majority of survivors are left with serious sequelae. Of those born without symptoms, ~15% develop sequelae of mental retardation or sensorineural hearing loss during follow-up [reviewed by Stagno, 1990]. Given these figures and prospective studies showing that the rate of congenital infection is ~1% in the United States [Demmier, 1991] and 0.3% in the United Kingdom [Peckham et al., 1983], it is possible to estimate the annual public health impact of congenital CMV infection (see Table I). These estimates show CMV to be second only to Down's syndrome as a known cause of mental retardation and indicate that finding means to control its pathogenicity would be well worthwhile.

A series of studies have investigated the effect of primary maternal CMV infection on the fetus [Stern and Tucker, 1973; Grant et al., 1981; Ahlfors et al., 1982; Griffiths and Baboonian, 1984; Kumar et al., 1984; Stagno et al., 1986; Yow et al., 1988]. Overall, 1.3% of initially seronegative women seroconvert dur-
TABLE I. Annual Public Health Impact of Congenital CMV*

<table>
<thead>
<tr>
<th></th>
<th>United States</th>
<th>United Kingdom</th>
</tr>
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<tbody>
<tr>
<td>No. of births</td>
<td>4,000,000</td>
<td>700,000</td>
</tr>
<tr>
<td>Rate of congenital infection (%)</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>No. with congenital infection</td>
<td>40,000</td>
<td>2,100</td>
</tr>
<tr>
<td>No. with CID* (7%)</td>
<td>2,800</td>
<td>147</td>
</tr>
<tr>
<td>No. of fatalities (12%)</td>
<td>336</td>
<td>18</td>
</tr>
<tr>
<td>No. with sequelae (30%)</td>
<td>2,218</td>
<td>132</td>
</tr>
<tr>
<td>No. with asymptomatic (93%)</td>
<td>37,200</td>
<td>1,953</td>
</tr>
<tr>
<td>No. with sequelae (15%)</td>
<td>5,580</td>
<td>293</td>
</tr>
<tr>
<td>Total sequelae or death</td>
<td>8,134</td>
<td>443</td>
</tr>
</tbody>
</table>

*After Stagoon [1990].
*CID, cytomegalic inclusion disease.

strains of CMV has shown that re-infection with donor strains of virus has distinct pathological potential [Grundy et al., 1988].

In contrast, with bone marrow allograft patients, CMV disease usually arises from reactivation of latent infection in the recipient [Winston et al., 1985]. Furthermore, when the donor marrow is depleted of T cells, there appears to be a lower incidence of CMV disease when the donor is seropositive (see Table II). We take these findings to indicate that adoptive transfer of immunity may occur at the time of transplantation from the immunocommitted donor marrow [Wimperis et al., 1986]. The process of T-cell depletion in addition to decreasing grafted vs. host disease presumably removes those cells that would otherwise transmit CMV, since centres that do not perform depletion report that donor marrow can be a source of CMV.

AIDS Patients

Since most HIV-positive individuals are also CMV IgG positive, it is likely that reactivation of latent virus is a major source of CMV infection. However, multiple strains of CMV have been described in populations at risk [Drew et al., 1984], so re-infection remains a possibility that has not been formally evaluated.

Most cases of CMV disease present as retinitis (85%) or gastrointestinal ulceration (15%), usually once the CD4 count has declined below 100 × 10^6/liter [Gallant et al., 1992]. There is no evidence for CMV causing pneumonitis in AIDS patients [Millar et al., 1990], despite the presence of CMV in the lungs, presumably because the lungs cannot mount the T-cell response required for immunopathology (see below).

HIV-Positive Individuals

In contrast to the above-mentioned examples of CMV acting as an opportunist, it has been reported in a population of HIV-infected haemophiliacs that those also infected with CMV develop AIDS significantly (relative risk 3.2; P = 0.003) more rapidly than those without CMV infection [Webster et al., 1989]. This effect was statistically independent of age (relative risk 2.5; P = 0.02) and was accompanied by increased presence of p24 antigen, suggesting that CMV was working by driving HIV replication. Further studies are required in other populations to evaluate this relationship and to determine which, if any, of the mechanisms described below is responsible for the observed phenomenon. None of the patients in the haemophilia study had CMV as an AIDS-indicator disease, so an opportunistic relationship between CMV and HIV was not observed. This illustrated that a cofactor effect can be discerned clearly only if opportunism is first excluded. As a corollary to this, it can be concluded that any survival benefit of a treatment established in a controlled trial can be ascribed only to suppression of a cofactor if opportunism by the same virus is shown to be unaffected by the drug under study.

Organ Transplant Recipients

CMV infection is found frequently in allograft recipients, but not all infected individuals will develop disease (see Table II). In recipients of solid organs, disease is found largely when a seropositive organ containing the virus is transplanted into a recipient. If the recipient has pre-existing immunity against CMV, this can ameliorate the disease, but only partially. Typing of
PATHOGENESIS

CMV infection in many cells of the body causes no symptoms. In others, it may cause lysis of the target cells and so is amenable potentially to antiviral chemotherapy. An example is CMV infection of the retina, which responds moderately well to ganciclovir or foscarnet. Likewise, active infection of marrow stromal cells may provide an unfavourable environment for haematopoiesis [Apperley et al., 1989]. In contrast, there is now extensive evidence from both the mouse and man to suggest that the pathogenesis of CMV pneumonia is immunopathologically mediated [Grundy et al., 1987]. Under these circumstances, administration of an antiviral drug would be expected to have only minimal effects, so therapy should be directed towards modulation of the immunopathological response.

As was described above, there is also evidence that CMV can act as a cofactor to enhance the pathogenicity of HIV. Such interaction might take place at the cell-to-cell level, where presentation of CMV antigens to an immune cell harbouring latent HIV could lead to activation of HIV. Likewise, the release of cytokines from bystander immune cells could drive HIV replication in neighbouring cells [Clouse et al., 1989]. Interactions could also occur at the single cell level, for example, transactivation of the HIV genome by CMV immediately-early proteins [Ghazal et al., 1991]. CMV could also increase the tropic range of HIV by expressing its Fc receptor on cells and so allowing opsonised HIV to gain entry to a new group of tissues or by forming pseudotypes between the two viruses [McKeating et al., 1990].

DIAGNOSIS

Since most of the patients who suffer from CMV disease are immunocompromised, it is inappropriate to use serological methods for diagnosis [Pass et al., 1983; Paya et al., 1989]. Over the past decade, several different ways of using monoclonal antibodies to detect CMV in body fluids have been described so that next-day diagnosis of CMV infection should now be routine [Griffiths et al., 1984; Gleaves et al., 1984; van der Bij et al., 1988; Revello et al., 1989]. The polymerase chain reaction offers the potential of high sensitivity and rapidity and is being evaluated at several centres.

To date, only two methods (conventional cell culture and detection of early antigen fluorescent foci) have been shown to provide prognostic information when used prospectively to test surveillance cultures from bone marrow transplant patients [Meyers et al., 1990; Webster et al., 1992]. It will be important for newer methods such as polymerase chain reaction to be evaluated with the same degree of vigour.

TREATMENT

There are four main strategies for the use of drugs against CMV. Prophylaxis with several agents has shown encouraging results. Back in 1979 [Cheesman et al., 1979] and again in 1983 [Hirsch et al., 1983], workers in Boston reported that leucocyte interferon could delay the median time to CMV excretion and reduce either viraemia or CMV syndromes, respectively, in renal allograft recipients. We have recently completed a trial in 68 similar patients using the same protocol and can confirm the results [Lui et al., 1992].

In 1988, high-dose intravenous acyclovir was shown to provide protection for bone marrow transplant patients when given 5 days before to 30 days after bone marrow transplant [Myers et al., 1988]. However, the patients in this group were not randomly allocated to receive acyclovir but were selected on the basis of their serological status for CMV and HSV. This led to some doubt about the validity of the results, although in the following year, when Balfour et al. [1989] reported that high-dose oral acyclovir could significantly reduce CMV disease in renal transplant patients, it became clear that acyclovir was a useful prophylactic agent for CMV disease. This is true despite the fact that the dose required to inhibit 50% of the replication of laboratory strains in cell culture exceeds the concentration attainable in plasma of patients [Balfour et al., 1989]. This shows that the plasma levels of drug obtained are poorly reflective of the situation in vivo and that further studies are required to define the level, particularly of acyclovir triphosphate, found in target cells for CMV replication. A recent placebo-controlled trial of ganciclovir in heart transplant recipients showed significant clinical and virological benefit [Merigan et al., 1992]. Two studies in bone marrow transplant patients
have shown that ganciclovir prophylaxis, begun after marrow engraftment, can significantly reduce CMV infection [Goodrich et al., 1993; Winston et al., 1993] and CMV disease [Goodrich et al., 1993]. Patients in the latter trial received a higher daily dose of ganciclovir and received high-dose acyclovir until the marrow had engrafted. Neither study showed improved patient survival.

**Suppression** has so far been described for one trial in bone marrow transplant patients given ganciclovir if CMV excretion was found at any site [Goodrich et al., 1991]. The drug was given until 100 days posttransplant, and a significant reduction in CMV disease at this time and also at day 180 was noted. However, the patients in the study represented only a subgroup of those followed, so many of the total population would not be eligible to benefit from suppressive therapy.

**Preemptive therapy** has been used for bone marrow transplant patients whose routine bronchial lavage on day 35 postbone marrow transplant showed CMV [Schmidt et al., 1991]. Compared to those allocated to no treatment, ganciclovir showed a reduced development of CMV pneumonitis or death. However, it should be noted that not all patients in this cohort destined to develop CMV pneumonitis were detected by the bronchial lavage procedure at day 35.

**Treatment** of established disease has been attempted with a variety of investigational drugs for CMV pneumonitis in bone marrow transplant patients [reviewed by Reed et al., 1988]. None of these open studies provided any encouraging results despite in some cases having good control of virus replication, as measured in serial lung biopsies. Two open studies recently suggested that the combination of ganciclovir and immunoglobulin can increase the number of survivors [Reed et al., 1988; Emanuel et al., 1988]. Given the pathogenesis of this condition, described above, we would suggest that the immunoglobulin has an immunomodulatory effect. Clearly, controlled trials are required, and a comparison of equivalent doses of immunoglobulin preparations from CMV seropositive and seronegative individuals would be informative.

One placebo-controlled trial of ganciclovir for treatment of established gastrointestinal CMV infection has been reported [Reed et al., 1990]. Although ganciclovir suppressed CMV excretion, no clinical benefit was observed from the 2 week course given.

A controlled comparison of ganciclovir against foscamet for induction and then maintenance therapy of CMV retinitis in AIDS patients has recently been described [Studies of Ocular Complications of AIDS Research Group, 1992]. Both drugs were equally effective in suppressing CMV retinitis, but patients receiving foscamet had a significant survival benefit. There are several possible reasons for the decreased mortality seen. It may be statistical, that in the complex allocation of patients within particular strata led to fewer patients being allocated to foscamet, or the results may represent imbalanced receipt of antiretroviral therapy, although the authors could find no evidence for this.

### Table III. Suggested Treatment of CMV (1992)*

<table>
<thead>
<tr>
<th>Site infected</th>
<th>Transplant</th>
<th>AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine or saliva</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Blood</td>
<td>GCV</td>
<td>GCV?</td>
</tr>
<tr>
<td>Lung</td>
<td>Ig + GCV</td>
<td>None</td>
</tr>
<tr>
<td>Retina</td>
<td>GCV</td>
<td>Fos + maint</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>GCV</td>
<td>GCV</td>
</tr>
</tbody>
</table>

*Abbreviations: GCV, ganciclovir; Fos, foscarnet; Ig, immunoglobulin; maint, maintenance therapy.

Alternatively, the improved mortality may have a biological explanation in that foscarnet has some activity against HIV, or it may be more able to suppress the CMV cofactor effect than ganciclovir. All these results can be tabulated summarising the author's current advice about the treatment of CMV infection in particular groups of patients (see Table III).

Strains of CMV resistant to ganciclovir [Erici et al., 1989] and to both ganciclovir and foscarnet [Knox et al., 1991] have been described. The clinical significance of such isolates is undefined. The possibility of inadequate response to therapy being due to the development of resistance is still managed on clinical criteria. In the author's opinion, assays able to alert clinicians in a timely manner to the development of resistance are urgently required.

### References


