Failure of Adjunctive Cytomegalovirus Intravenous Immune Globulin To Improve Efficacy of Ganciclovir in Patients with Acquired Immunodeficiency Syndrome and Cytomegalovirus Retinitis: a Phase 1 Study

MARK A. JACOBSON,1,2* JAMES J. O'DONNELL,3,4 RALPH ROUSELL,5 BARBARA DIONIAN,1 AND JOHN MILLS V1,2

The Medical Service1 and The Ophthalmology Service,3 San Francisco General Hospital, San Francisco, California 94110; Department of Medicine2 and Department of Ophthalmology,4 University of California San Francisco, San Francisco, California 94143; and Cutter Biological, Miles Inc., Berkeley, California 94707

Received 22 August 1989/Accepted 24 October 1989

Six men with acquired immunodeficiency syndrome (AIDS) and cytomegalovirus (CMV) retinitis, treated with combined ganciclovir induction therapy and hyperimmune globulin (CMV-IGIV) for 10 days followed by CMV-IGIV alone, had a median time to retinitis progression shorter (7 days) than had eight historical controls given ganciclovir maintenance therapy (54 days; \( P = 0.06 \)) and similar to that in eight controls given ganciclovir for 10 days only (19 days; \( P = 0.97 \)). CMV-IGIV, which also failed to inhibit CMV replication in blood and urine, did not appear to add markedly to the efficacy of ganciclovir in acquired immunodeficiency syndrome-associated CMV retinitis.

Cytomegalovirus (CMV) retinitis is a sight-threatening opportunistic infection affecting at least 6% of patients with acquired immunodeficiency syndrome (AIDS) (8). Several clinical studies have reported that therapy with ganciclovir results in the stabilization of CMV retinitis (2, 6–8). Since most of these patients have progressive retinal necrosis within 1 month after ganciclovir therapy is discontinued, life-long daily ganciclovir therapy is required (2, 6, 8).

Intravenous immune globulin prepared from donors with high titer of antibody to CMV (CMV-IGIV) has been used in the prophylaxis of CMV pneumonitis complicating allogeneic bone marrow transplantation (3). In addition, two open prospective studies have suggested that ganciclovir combined with either CMV-IGIV or conventional IGIV administered to bone marrow transplant patients with life-threatening CMV pneumonitis results in improved survival as compared with that of historical controls treated with ganciclovir or CMV-IGIV alone (4, 9, 10; E. C. Reed, R. A. Bowden, P. S. Dandliker, and J. D. Meyers, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 731, 1986).

An alternative to daily intravenous ganciclovir maintenance therapy for CMV retinitis would be desirable, since this treatment causes serious neutropenia (absolute neutrophil count, <800 cells per \( \mu l \)) in 30% of patients and carries a risk of indwelling catheter-associated bacteremia (8). Hence, we performed a phase 1 study of combined ganciclovir and CMV-IGIV therapy for 10 days followed by biweekly CMV-IGIV infusions in AIDS patients with newly diagnosed CMV retinitis and compared the results with those for recent historical control patients from the same institution and treated with ganciclovir alone (8).

Criteria for CMV retinitis diagnosis were typical retinal opacity documented by indirect ophthalmoscopy, no other likely explanation of retinal findings, and no prior therapy with ganciclovir or foscarnet. Informed consent was obtained from all patients before study entry per local institutional review board guidelines.

Intravenous therapy consisted of a 10-day course of ganciclovir (5 mg/kg intravenously every 12 h) (Syntex Research, Palo Alto, Calif.). CMV-IGIV (Cutter Biological, Miles Inc., Berkeley, Calif.) was administered once (400 to 500 mg/kg) on days 1 to 3, again (400 mg/kg) on days 8 to 10, and subsequently (400 mg/kg) once every 2 weeks. CMV-IGIV is a sterile solution of immune globulin prepared by the Cohn method of cold ethanol fractionation of pooled human plasma selected from donors with high-titer antibodies to human CMV and contains 50 mg of protein per ml of solution with a pH of 4.25 and maltose added to achieve isotonicity. CMV-IGIV infusions were initiated at a rate of 0.02 ml/kg per min, gradually increased as tolerated to a rate of 0.08 ml/kg per min, and completed over a period of 3 to 5 h.

The extent of CMV retinitis was assessed by serial indirect ophthalmoscopic exams, retinal photographs, and best-corrected visual acuity measurements. The progression of retinitis in study subjects (group A) was compared with that in eight historical controls treated at the same institution with ganciclovir induction therapy (2.5 mg/kg every 8 h for 10 days) alone (group B) or eight historical controls treated at the same institution with induction therapy followed by daily ganciclovir maintenance therapy (5 mg/kg for 5 days per week) (group C) (8). Retinitis progression was defined as (i) a decrease in visual acuity by two lines or more, (ii) the appearance of a new retinal CMV exudate, or (iii) an increase in the size of a preexisting lesion by one disk diameter or more or such that it crossed a major vessel or entered a new sector of the retina (sectors are formed by the intersection of clock hours with ora serrata, equator, and posterior vascular arcades) when compared with results of the previous ophthalmoscopic exam (8). The same ophthalmologist performed all examinations.

Virologic response to therapy was assessed by biweekly cultures of urine and washed buffy coat blood specimens (8).

Between October 1987 and January 1989, six men with

* Corresponding author.
TABLE 1. Comparison of base-line characteristics of patients treated with ganciclovir plus CMV-IGIV (group A) and historical control patients treated with ganciclovir induction therapy only (group B) or ganciclovir induction therapy followed immediately by daily ganciclovir maintenance therapy (group C)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean hemoglobin (g/dl)</th>
<th>Mean absolute neutrophil count (cells/µl)</th>
<th>Median age (yr)</th>
<th>Median Karnofsky score</th>
<th>Median visual acuity in:</th>
<th>No. with previous episode of P. carinii pneumonia</th>
<th>Median time (mo) between first onset of P. carinii pneumonia and later treatment with ganciclovir</th>
<th>Mean absolute CD4+ lymphocyte count (cells/µl)</th>
<th>Median survival after CMV retinitis diagnosis (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>9.3</td>
<td>2,709</td>
<td>39</td>
<td>75</td>
<td>20/25/20</td>
<td>9/9</td>
<td>15/15</td>
<td>50/50</td>
<td>10/10</td>
</tr>
<tr>
<td>B</td>
<td>11.4</td>
<td>2,159</td>
<td>37</td>
<td>70</td>
<td>20/25/20</td>
<td>9/9</td>
<td>15/15</td>
<td>50/50</td>
<td>10/10</td>
</tr>
<tr>
<td>C</td>
<td>11.5</td>
<td>2,593</td>
<td>42</td>
<td>70</td>
<td>20/25/20</td>
<td>9/9</td>
<td>15/15</td>
<td>50/50</td>
<td>10/10</td>
</tr>
</tbody>
</table>

* NA, Not available.

AIDS and newly diagnosed CMV retinitis were enrolled in this study (group A). Base-line age, Karnofsky performance status, absolute neutrophil count, and visual acuity of these patients were similar to those of the two historical control groups (Table 1). However, patients treated with CMV-IGIV and ganciclovir tended to be more anemic and have more previous episodes of Pneumocystis carinii pneumonia occurring at a longer interval before the diagnosis of CMV retinitis.

All six study subjects completed the 10-day course of combined ganciclovir induction–CMV-IGIV therapy. Four patients continued biweekly CMV-IGIV maintenance therapy for an additional 14 to 64 days after completing induction therapy. The results of serial ophthalmoscopic evaluations are summarized in Table 2 and Fig. 1.

Prior to the initiation of study treatment, 9 of 12 (75%) urine and blood cultures from the six group A patients yielded CMV, as compared with 4 of 6 (67%) cultures obtained at the end of induction therapy from four patients and 7 of 11 (64%) cultures obtained during CMV-IGIV maintenance therapy from three patients (P > 0.1; Fisher exact test). Among the historical controls, the proportions of cultures from which CMV could be isolated decreased from 70% pretherapy to 19% at the end of ganciclovir induction therapy (P < 0.001), and only 9% of cultures obtained during daily ganciclovir maintenance therapy yielded CMV (P = 0.06) (8).

No acute toxicity was observed during CMV-IGIV infusions. During the study treatment period, hemoglobin decreased by >1 g/dl in patients 2 and 6, who had concurrent Mycobacterium avium complex disseminated infections, and the serum alanine aminotransferase increased ninefold in patient 1, who was receiving concurrent ketoconazole ther-

![FIG. 1. Time to retinitis progression in six patients treated with ganciclovir and CMV-IGIV (group A) as compared with that in eight historical controls treated with ganciclovir induction therapy alone (group B) or eight historical controls treated with ganciclovir induction therapy followed immediately by ganciclovir maintenance therapy (group C) (1). The median times to retinitis progression after completion of ganciclovir induction–CMV-IGIV therapy were 7 days in group A, 19 days in group B (P = 0.97; log-rank test), and 54 days in group C (P = 0.06; log-rank test).](http://aac.asm.org/content/177/3/1990.full)
therapy may have been more effective; however, we have not observed any difference in clinical efficacy when ganciclovir induction therapy alone has been administered as a 10- or 21-day regimen (M. Jacobson and J. Mills, unpublished data).

The underlying physiologic condition of the patients in the current study may have been worse than that of the historical controls, as evidenced by a lower hemoglobin and a more frequent history of prior P. carinii pneumonia in the current study patients (Table 1). However, their median survival was similar (4 months) to that of the historical controls treated with ganciclovir alone (5.4 months) (8).

The difference in the apparent efficacy of CMV-IGIV in AIDS-associated CMV retinitis and transplant-associated CMV pneumonitis may be due to a difference in the immunopathogenesis of these two diseases. There is clear evidence of an immunopathologic component of tissue injury in transplant-associated CMV pneumonitis, probably analogous to graft-versus-host disease (5). CMV-IGIV may act by reducing the extent of this immunopathologic injury. In contrast, necropsy histopathology studies of AIDS-associated CMV retinitis have shown a complete absence of inflammatory cells, suggesting that the retinal injury is due entirely to direct viral cytopathology (1). These findings may explain why, in this small pilot study, CMV-IGIV did not appear to add markedly to the efficacy of ganciclovir in AIDS-associated CMV retinitis.

We thank Cheryl Cox, William Buhles, Joanne Rush, Marti Nash, Debby Wong, and the staff of wards 5A, 4C, and 86 and the Ophthalmology Clinic of San Francisco General Hospital for their help in completing this study.

This study was partially supported by a grant from Cutter Biological, Miles Inc., Berkeley, Calif.

LITERATURE CITED