NEW CARDIOMYOPATHY: PILOT STUDY OF INTRAVENOUS GANCICLOVIR IN A SUBSET OF THE CHRONIC FATIGUE SYNDROME

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We describe a subset of patients with chronic fatigue syndrome (CFS) as defined by the CDC, a duration of overwhelming fatigue for <2 years, and oscillating repetitively abnormal T-waves at 24-hour electrocardiogram (ECG) recordings (Holter monitors). Baseline 12-lead ECG, 2-D echocardiogram, rest/stress myocardial perfusion (thallium 201 or TC-99 sestamibi) and rest/stress multiple-gaited acquisition studies, as well as coronary angiography excluded coronary artery disease. Patients in this CFS subset had significant Ig (with or without positive IgM) human cytomegalovirus enzyme-linked immunoassay antibody titers. They had little or no evidence of concurrent Epstein-Barr virus (EBV) multiplication, corroborated by negative viral capsid antigen IgM antibody titer and an EBV total early antigen antibody titer of ≤40. Patients were given intravenous ganciclovir (5 mg/kg q12h for 30 days). Before this treatment, none of 18 patients could work or manage a household. At evaluations, 24 weeks after ganciclovir, 13 patients (72%) returned to their premorbid healthy states (P <.05). There were no adverse effects from ganciclovir in these nonimmunosuppressed patients.

CHRONIC FATIGUE SYNDROME (CFS) is a disorder the natural history, clinical characteristics, pathologic physiology, and treatment of which remain uncertain [1]. Various hypotheses propose neuroendocrine or immunologic abnormalities or viral infections, including Epstein-Barr virus (EBV), human herpesvirus 6, and several enteroviruses and retroviruses [2]. There have been several studies of treatments [3-5]. Since the fatigue of the mononucleosis syndrome [6-8] resembles that of the CFS [9], we assayed antibodies to human cytomegalovirus (HCMV) and Epstein-Barr virus. High antibody titers to toxoplasmosis, an occasional cause of the mononucleosis syndrome [10], are unusual in CFS patients.

Rowe and colleagues [11] described seven nonsyncopeal adolescents presenting with fatigue and light-headedness and demonstrated abnormal responses to upright tilt. They followed this work with a prospective, nonselected, nonblinded study confirming a strong association between neurally mediated hypotension and CFS [12]. An abnormal response to upright tilt was observed in 22 of 23 patients with CFS vs. four of 14 controls (P <.001). Open, nonblinded, noncontrolled therapy directed at this abnormal reflex with fludrocortisone, β-adrenergic blocking agents and disopyramide appeared beneficial in this nonblinded trial. The authors concluded that neurally mediated hypotension is a cause of the symptoms of CFS or that it is strongly associated with another important etiologic factor.

We reported in 1993 that repetitively oscillating abnormal T-wave inversions and/or T-wave flats during 24-hour electrocardiogram (ECG) monitoring are present in patients with CFS, ECG abnormalities that
are nonspecific but seen less frequently in non-CFS patients \( (P < .01) \) [13]. Abnormal left ventricular myocardial dynamics are present in a cohort of patients with CFS. Decreased and/or flat ejection fractions with stress, abnormal wall motion at rest and stress, dilatation of the left ventricle, and segmental wall motion abnormalities are observed [14]. We now report a subset of CFS patients with (1) high human cytomegalovirus (HCMV) IgG enzyme-linked immunoassay antibody titers (ELISAs), (2) minimal or no serologic evidence of concurrent EBV multiplication, and (3) oscillating ECG abnormalities at Holter monitoring. We performed a pilot study to assess the possible efficacy of ganciclovir, an antiviral nucleoside useful in the treatment of several HCMV infections in immunosuppressed patients [15].

Methods

Patients. From March 1993 through June 1994, three men and 15 women (mean age, 39.7 ± 7.7 years) with CFS using CDC criteria were recruited from a single infectious diseases referral center in Birmingham, Michigan. Approximately 50 patients with CFS were screened for inclusion in this study. Demographics, including clinical and laboratory information, were obtained for all patients. HCMV ELISA IgM (Detroit Biomedical Laboratories, Detroit, Michigan) and HCMV ELISA IgG titers (Metpath Laboratories, Teterboro, New Jersey), as well as EBV capsid antigen (VCA), ELISA IgM, and EBV total early antigen (EA) immunofluorescent antibody titers (Roche Laboratories, Columbus, Ohio) were assayed [16,17]. Buffy coats, urines, and myocardial biopsies were tested for infectious HCMV.

As a control of the occurrence of HCMV and EBV antibodies in normal non-CFS persons (Results, Group C) residing in this same area, 20 randomly chosen well individuals were tested for HCMV, IgM, and IgG antibodies and for EBV VCA IgM, and EA antibodies. Results of Holter monitoring, stress multiple-gaited acquisition (MUGA) studies and endomyocardial biopsies in these patients have been described [13–14,18].

Holter monitors, MUGA studies, and endomyocardial biopsies were read blindly (without knowledge of the patient). All such readings were repeated by at least one, and often several, other physician-readers. Each CFS patient had a normal 12-lead standard ECG and a normal 2-D echocardiogram, except for occasional mitral valve prolapse. Mitral valve prolapse without significant mitral valve insufficiency does not cause abnormal T-wave oscillations at Holter monitoring [19]. As previously, 24-hour continuous ECGs were obtained using a modified standard lead I and precordial lead V₅ [13]. A patient's 24-h Holter monitor was considered positive if T-waves became intermittently inverted or flat, i.e., the T-waves were below the horizontal described by inceptions of p and Q waves in one of the two monitored leads with two or more episodes for at least 25.0 normally conducted QRS complexes. A uniformly flat T-wave (isoelectric) was considered positive. T-waves were evaluated independent of possible ST segment changes. Biphasic T-waves were considered normal. U waves (a small, shallow, positive, rounded deflection inscribed immediately after the T-wave) did not interfere with this analysis. Labile T-wave abnormalities at Holter monitoring were present in each CFS patient.

Energy index. At each outpatient visit, a subjective evaluation of the patient's functional status was recorded. The Energy Index (EI) is defined as 10 when the patient is well. The EI records the average subjective vitality of the patient in the immediate 14 days before the specific outpatient visit. When minor illnesses (e.g., rhinovirus infection, sinusitis) complicated a visit, evaluation of the EI for a patient was delayed until the intercurrent problem receded. A CFS patient with an EI of 0 is bedridden. A CFS patient with an EI of 5 can work, provided his or her work is sedentary. Patients with EIs of <5 cannot perform a 40-hour a week job. Before the initiation of intravenous ganciclovir and, again, 6 months later, objective evaluations of the ability to work and the EI for each study patient were analyzed. At these times, the patient was either fully engaged in his or her premorbid activity at work or home (e.g., active homemaker), or he or she had not returned to the premorbid occupation.

Validation of EI for the severity of the chronic fatigue syndrome. Grade 0: Patients are confined to bed by number and severity of symptoms listed below.

Grades 1–2: Any activity leads to overwhelming, incapacitating fatigue. Patients are light-headed, unable to think clearly, concentrate, or read for any extended period (over 60 minutes). Left-sided chest aches, palpitations, sore throats, and feverishness are frequent. Patients can be out of bed only for intermittent, brief parts of each day.

Grades 3–5: With great effort, patients can be out of bed and perform nonphysical activities for several hours each day. Any exertion markedly worsens fatigue. Patients variably express lightheadedness and inability to think clearly or read normally. Left-sided chest aches, palpitations, sore throats, and feverishness are frequent. Patients cannot perform a 40-hour a week
of these patients had had psychiatric illness before the
virus. Patients in both CFS groups A and B experienced
depressions, which sometimes accompany CFS. None of
patients. Before receiving intravenous ganciclovir,
chloride were given for insomnia or severe reactive
longer in group B (2.8 years) than in group A (1.6
years). Temazepam (15 mg) and/or fluoxetine hydro-
alcohol. A regular sleeping pattern was encouraged. As
needed, temazepam (15 mg) and/or fluoxetine hydro-
cloride were given for insomnia or severe reactive
depressions, which sometimes accompany CFS. None of
these patients had had psychiatric illness before the
onset of CFS. After completion of ganciclovir, patients
were encouraged to renew normal activities in gradual
increments as tolerated. They were asked to not exer-
cise until 6 months after completion of ganciclovir.

Cardiac, virologic, and electron microscopic studies.
Twelve-lead ECG, 2-D echocardiography, Holter mon-
toring, and stress MUGA studies were performed on
each patient. Myocardial perfusion rest/stress (thallium
201 or TC-99 sestamibi) studies were performed on 14
patients. Coronary angiograms were performed when
indicated to exclude coronary artery disease. Right ven-
tricular endomyocardial biopsies were performed in
seven patients. Cardiac tissues were cultured in tissue
culture for the presence of infectious HCMV. Another
section of the biopsy was taken immediately in 2.5%
cacodylate buffered glutaraldehyde, postfixed in 1%
-osmium tetroxide, and embedded in Epon 812. Thin
sections for electron microscopy were stained with
uranyl acetate, followed by lead citrate.

Statistical methods. Eighteen patients (three men and
15 women) whose mean age was 39.7 years (range,
29–51 years) were enrolled. Therapeutic efficacy could
be determined for all patients. Follow-up information
at 6 months posttherapy was available for all patients.
Statistical significance between patients meeting the
criteria for the HCMV subset and other patients with
CFS was evaluated using tests of homogeneity of odds,
$\chi^2$ analysis, and the two-tailed Fisher's exact test for
bivariate analysis of dichotomous data. Continuous
variables were compared with the Wilcoxon rank sum
test. Differences in EBV and EA antibody titers between
groups A, B, and C were tested by $\chi^2$ analysis.

Results

Demographics. Demographic findings and outcomes
are shown in Table 1. Thirteen patients improved. The
non-CFS control (group C) is a random group of well
persons. The gender and ages of CFS patients who
improved (group A, 13 patients) and the other CFS
patients who did not (group B, five patients) were
similar. Groups A, B, and C were mostly women. Mean
ages were 37 years (group A), 41 years (group B), and
32 years (group C). Patients in groups A and B had no
known preexisting chronic illnesses. One patient each
in group A and B smoked, and a single patient in group
A had an elevated cholesterol level (265 mg/dL).

The mean duration of fatigue before therapy was
longer in group B (2.8 years) than in group A (1.6
years) patients. Before receiving intravenous ganciclo-
vir, patients in both CFS groups A and B experienced
TABLE 1. Clinical findings in 18 CFS patients treated with intravenous ganciclovir

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improved</td>
<td>Not improved</td>
<td>Non-CFS controls</td>
</tr>
<tr>
<td></td>
<td>(n=13)</td>
<td>(n=5)</td>
<td>(n=20)</td>
</tr>
<tr>
<td>Demographic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>10 women</td>
<td>5 women</td>
<td>12 women</td>
</tr>
<tr>
<td></td>
<td>3 men</td>
<td>0 men</td>
<td>8 men</td>
</tr>
<tr>
<td>Age (y)</td>
<td>37 (mean), 41 (median), 29-51 (range)</td>
<td>41 (mean), 45 (median), 31-49 (range)</td>
<td>32 (mean), 32 (median), 20-48 (range)</td>
</tr>
<tr>
<td>Risk factors for ischemic heart disease</td>
<td>1 patient, smoker; 1 patient, elevated cholesterol</td>
<td>1 patient, smoker</td>
<td></td>
</tr>
<tr>
<td>Symptoms/signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of fatigue (y)</td>
<td>1.6 (mean), 1.3 (median), 0.3-5.0 (range)</td>
<td>2.8 (mean), 2.0 (median), 0.9-6.0 (range)</td>
<td>Not fatigued</td>
</tr>
<tr>
<td>Marked worsening of fatigue at exercise</td>
<td>13 of 13 patients</td>
<td>5 of 5 patients</td>
<td>Non-CFS random persons</td>
</tr>
<tr>
<td>Myalgia</td>
<td>12 of 13 patients</td>
<td>3 of 5 patients</td>
<td>Non-CFS random persons</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>8 of 12 patients</td>
<td>4 of 5 patients</td>
<td>Non-CFS random persons</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>8 of 13 patients</td>
<td>2 of 5 patients</td>
<td>Non-CFS random persons</td>
</tr>
<tr>
<td>Chest ache</td>
<td>7 of 13 patients</td>
<td>4 of 5 patients</td>
<td>Non-CFS random persons</td>
</tr>
<tr>
<td>Depressed, taking antidepresant medicine</td>
<td>4 of 13 patients</td>
<td>1 of 5 patients</td>
<td>Non-CFS random persons</td>
</tr>
<tr>
<td>Complete physical examination, negative</td>
<td>10 of 13 patients</td>
<td>3 of 5 patients</td>
<td>Non-CFS random persons</td>
</tr>
</tbody>
</table>

Note. Abbreviation used: CFS, chronic fatigue syndrome.

* Two patients had murmurs of mitral insufficiency, and a third had an occasional asthmatic episode.

* Two patients had euthyroid goiters.

marked worsening of fatigue with exercise. Myalgia; lightheadedness; and dull, nonspecific left-sided chest aches not related to activities were noted in both CFS groups. Physical examinations were normal in all patients except as noted. Two group A patients had mitral valve prolapse; another group A patient had an occasional mild episode of bronchial asthma. Euthyroid goiters were present in two group B patients. Reactive depressions were more common in group A. Eight group A and two group B patients complained of difficulty concentrating.

Cardiac studies. Results of cardiac tests are shown in Table 2. Twelve-lead ECGs were normal except for single lead T-wave inversions in standard lead III (seven patients, group A; 2 patients, group B). Two-dimensional echocardiograms (both groups) were generally unremarkable. Mitral valve prolapse was found in three patients (two patients, group A; one patient, group B). Every patient in groups A and B showed abnormal T-wave oscillations by Holter monitoring [13]. Myocardial perfusion rest/stress studies (thallium-201 or TC-99 sestamibi) were normal in 13 of the 14 patients (groups A and B) on whom this study was performed. Two patients, one from each group, had normal coronary angiograms. One 41-year-old millwright (see Case Report) from Group A had a normal coronary angiogram but with exercise demonstrated reversible “ischemia” of the anterior apical and inferior walls [18]. At right ventricular endomyocardial biopsy, varying degrees of cardiomyopathic changes (Figure 1) characterized by myofiber disarray, myofiber dissolution, myofiber dropout with fibrous replacement, and occasional myofiber hypertrophy were evident (five group A patients, two group B patients). Cultures of cardiac tissues for infectious HCMV were negative.

Abnormal myocardial dynamics by MUGA rest/stress studies were present in six of 13 patients (group A). Two patients had reduced ejection fractions (EFs) at rest (40% and 45%); another patient had an EF that decreased during exercise from 51% to 36%. Two patients demonstrated tardokinetic; three showed hypokinesis, and four displayed left ventricular dilatation. No patient in group B had abnormal ventricular dynamics. A normal resting left ventricular EF at stress MUGA study is ≥50%. With exercise, the EF normally rises ≥5%. A stationary or falling EF is abnormal. The variability of results of this test in our nuclear medicine department is 5%. All MUGA studies were read blindly by at least two subspecialist nuclear medicine physicians without any knowledge of this study. These MUGA study changes are not seen in normal persons leading a sedentary life. Deconditioning and a seden-
TABLE 2. Cardiac findings in 18 CFS patients treated with intravenous ganciclovir

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twelve-lead ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated T-wave inversion, lead III</td>
<td>7 of 13 patients</td>
<td>2 of 5 patients</td>
</tr>
<tr>
<td>T-flat in lead III</td>
<td>0 of 13 patients</td>
<td>1 of 5 patients</td>
</tr>
<tr>
<td>2-D echocardiogram, normal</td>
<td>10 of 13 patients^*</td>
<td>3 of 5 patients^*</td>
</tr>
<tr>
<td>Repetitively changing normal to flat/inverted T-waves at Holter monitor</td>
<td>13 of 13 patients</td>
<td>5 of 5 patients</td>
</tr>
<tr>
<td>Myocardial perfusion rest/stress study (thallium-201 or TC-99 sestamibi, normal)</td>
<td>10 of 11 patients^*</td>
<td>3 of 3 patients</td>
</tr>
<tr>
<td>Coronary angiogram, normal</td>
<td>2 of 2 patients</td>
<td>1 of 1 patient</td>
</tr>
<tr>
<td>Cardiomyopathy, at biopsy</td>
<td>5 of 5 patients</td>
<td>3 of 3 patients</td>
</tr>
<tr>
<td>Abnormal MUGA, rest/stress study Initial</td>
<td>6 of 13 patients</td>
<td>0 of 5 patients</td>
</tr>
<tr>
<td>After intravenous ganciclovir at 6-month visit</td>
<td>3 of 6 patients</td>
<td>1 of 4 patients</td>
</tr>
</tbody>
</table>

Note. Abbreviations used: CFS, chronic fatigue syndrome; ECC, electrocardiogram; MUGA, multi-gated acquisition.

^* Two patients had mitral valve prolapse, and another had mild left ventricular enlargement.

^ One patient had mitral valve prolapse, and a second had mild tricuspid insufficiency.

^ One patient with a normal coronary angiogram showed reversible ischemia at anterior, apical, and inferior walls with exercise. This patient is described in the Case Report (see text).

Tertiary life in normal patients are not causes of decreased or falling left ventricular EFs [21].

After treatment with ganciclovir, three patients (group A) with previously abnormal myocardial dynamics reverted to normal; in three others (group A), results of MUGA tests improved with lesser degrees of tardokinesis, hypokinesis, or left ventricular dilatation. At follow-up 6 months after intravenous ganciclovir, one patient (group B) with an initial normal rest/stress MUGA study showed septal hypokinesis.

**HCMV and EBV antibody titers.** Patients in group A (Table 3) had high HCMV ELISA IgG antibody titers (mean, 322 U; median 204 U; range 120-503 U). Two patients (group A) had positive HCMV IgM antibody titers (Table 3). No patient (group A) had demonstrable IgM antibody titers to EBV VCA: 10 of the 13 patients had little or no evidence of EBV multiplication as tested by an elevated antibody titer to EA (EBV EA titer ≤40).

A somewhat different serum antibody profile was seen in patients from group B. Three of these five patients had no antibody to HCMV. One patient had a transient HCMV IgM titer. We suspect that this was a false-positive test because at repeated testing, the HCMV ELISA IgG titer was negative. Active EBV multiplication was more common in CFS patients in group B. EBV IgM titers were present in two patients, and the EBV EA titer was 320 in a third patient. Using χ² analysis, no statistical difference in HCMV IgM antibody titers was present between group A and group B. With the Wilcoxon rank sum test, HCMV IgG titers had higher values in group A compared with group B (P = .015). For EBV VCA IgM (χ² analysis) and EBV EA (rank

**FIGURE 1.** Top, a 30-year-old woman (group A). There is localized resolution of myofibrils (arrow), and the area is replaced by abundant glycogen granules admixed with endoplasmic reticulums, mitochondria, and residual myofibrils (lead citrate, magnification ×7275). Bottom, a higher magnification of the area (open arrow; see A) shows residual myofibrils in a haphazard arrangement, admixed with abundant glycogen granules (lead citrate, magnification ×36,900).
**TABLE 3. Antibody titers to HCMV and EBV in 18 CFS patients treated with intravenous ganciclovir**

<table>
<thead>
<tr>
<th>Antibody titer</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improved (n = 13)</td>
<td>Unchanged (n = 5)</td>
<td>Non-CFS controls</td>
</tr>
<tr>
<td>HCMV IgG at onset of ganciclovir</td>
<td>322 (mean)/422 (mean);</td>
<td>125 (mean)/100 (mean);</td>
<td>240 (mean);b</td>
</tr>
<tr>
<td>6 months later</td>
<td>204 (median)/352 (median);</td>
<td>negative (median)/negative (median);</td>
<td>188 (median); negative to 673 (range)</td>
</tr>
<tr>
<td></td>
<td>120–503 (range)/</td>
<td>negative to 368 (range)/negative (range)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>116–635 (range)</td>
<td>to 265 (range)</td>
<td></td>
</tr>
<tr>
<td>HCMV IgM positive at onset of</td>
<td>2 of 3 patients/0 of 8</td>
<td>1 of 5 patients/0 of 5</td>
<td>1 of 20 persons</td>
</tr>
<tr>
<td>ganciclovir/6 months later</td>
<td>patients</td>
<td>patients</td>
<td></td>
</tr>
<tr>
<td>EBV at onset of ganciclovir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCA IgM positive</td>
<td>None of 7 patients/not done</td>
<td>2 of 5 patients/not done</td>
<td>1 of 20 persons</td>
</tr>
<tr>
<td>EA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>11 of 13 patients</td>
<td>4 of 5 patients</td>
<td>20 of 20 persons</td>
</tr>
<tr>
<td>&lt;40</td>
<td>10 of 13 patients</td>
<td>3 of 5 patients</td>
<td>16 of 20 persons</td>
</tr>
<tr>
<td>&lt;20</td>
<td>7 of 13 patients</td>
<td>3 of 5 patients</td>
<td>15 of 20 persons</td>
</tr>
<tr>
<td>EA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>148/37</td>
<td>84/170</td>
<td>22</td>
</tr>
<tr>
<td>Median</td>
<td>40/0</td>
<td>20/0</td>
<td>Negative</td>
</tr>
<tr>
<td>Range</td>
<td>Negative to 1280/0–160</td>
<td>Negative to 320/negative to 640</td>
<td>Negative to 80</td>
</tr>
</tbody>
</table>

Note. Abbreviations used: HCMV, human cytomegalovirus; EBV, Epstein-Barr virus; CFS, chronic fatigue syndrome; VCA, viral capsid antigen; EA, early antigen.

- HCMV titers in group A patients are significantly higher than HCMV titers in group B (P <.015, Wilcoxon rank sum test).
- Fourteen (70%) of 20 normal (non-CFS) control persons had an IgG titer to HCMV.
- This test was not confirmed. The patient had repetitively negative IgG HCMV antibody titers. We suspect a false-positive IgM titer.
- Eleven (55%) of 20 normal (non-CFS) persons had negative antibody titers to EBV EA.

**Changes in vitality after intravenous ganciclovir.** At the start of ganciclovir, the severity of fatigue (EI) in all patients was similar (e.g., 3, mean grade, group A vs. 2, mean grade, group B). Six months later, the energy indices diverged. Mean EIs were grade 7 and grade 4 for groups A and B, respectively (Table 4). Before therapy with ganciclovir, no patient (group A or group B) could work or function normally (e.g., homemaker). After treatment with ganciclovir, the 13 patients from group A, but no patient from group B, returned to his or her premorbid activity. A repeat measures analysis of the EI values between cohorts indicated that patients in group A had greater improvement than those in group B (P <.05).

**Toxicities of intravenous ganciclovir.** A single patient (Group A) had a transient increase in serum creatinine.

**TABLE 4. Severity of fatigue in 18 CFS patients after intravenous ganciclovir**

<table>
<thead>
<tr>
<th>Energy index*</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of fatigue, first visit</td>
<td>3 (mean); 4 (median); 0–5 (range)</td>
<td>2 (mean); 2 (median); 0–4 (range)</td>
</tr>
<tr>
<td>Severity of fatigue, 6 months after</td>
<td>7 (mean); 7 (median); 5–9 (range)</td>
<td>4 (mean); 5 (median); 2–5 (range)</td>
</tr>
<tr>
<td>intravenous ganciclovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Able to perform premorbid activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at work or home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit</td>
<td>0 of 13 patients</td>
<td>0 of 5 patients</td>
</tr>
<tr>
<td>6 months after intravenous ganciclovir</td>
<td>13 of 13 patients</td>
<td>0 of 5 patients</td>
</tr>
</tbody>
</table>

Note. Abbreviation used: CFS, chronic fatigue syndrome.

- See Methods for definition.
- Energy indices in groups A and B are different (P <.05, repeat measures analysis).
She was obese, and when her ganciclovir dosage was recalculated on the basis of lean body mass, the serum creatinine reverted to normal. On repeated hematologic tests, biochemical tests, or urine studies, no other abnormalities were attributable to ganciclovir. Similarly, no adverse events or symptoms were attributable to ganciclovir. Ganciclovir was significantly less toxic in these nonimmunosuppressed CFS patients than in immunosuppressed cancer or AIDS patients [15]. We could find no previous experience in the literature on the expected toxicity of intravenous ganciclovir in normal persons, and there is no proven indication for ganciclovir in nonimmunosuppressed patients at this time.

Case Report

A 51-year-old millwright enjoyed excellent health. His only risk factor for coronary artery disease was cigarette smoking. Over several months, he experienced overwhelming, progressive fatigue that forced him to stop working on October 19, 1993. He could barely rise from his bed, and slight exertion further worsened his fatigue. He was lightheaded, had severe generalized muscle aches and an intermittent sore throat, and was unable to think clearly. Physical examination was normal except for a threefold enlarged nonnodular thyroid. Chest roentgenogram, CBC, total and high-density lipoprotein cholesterol, T3, T4, thyroid-stimulating hormone, SMA values, and urinalysis were normal. A resting 12-lead ECG showed an inverted T-wave in standard lead III but was otherwise normal. An HCMV ELISA IgM antibody titer was positive, and the IgG titer was 498 [18]. EBV VCA IgM and EBV EA tests were negative. Herpesvirus 6 IgM was negative; the herpesvirus 6 IgG ELISA was 160. Holter monitoring on September 4, 1993, showed oscillating, abnormal, flat or inverted T-waves appearing with the onset of sinus tachycardias and alternating with the reappearance of normal upright T-waves when tachycardias resolved. A 2-D echocardiogram showed minimal right ventricular hypertrophy consistent with bronchial asthma.

A myocardial perfusion rest/stress test TC-99 sestamibi on October 19, 1993, showed reversible "ischemia" of the anterior, apical, and inferior walls, but at cardiac catheterization, the coronary arteries were patent on October 21, 1993. A stress MUGA study on October 11, 1993, revealed abnormal left ventricular function. Resting EF was 40% (normal, \( \geq 50\% \)). The maximal exercise tolerance was 600 kg/min, at which time the EF increased to 54%. Myocardial biopsy on October 21, 1993, at electron microscopic study showed focal myofiber disarray and hypertrophy.

Beginning on October 20, 1993, the patient was given daily intravenous ganciclovir (5 mg/kg q12h) for 30 days. Nearly 5 months later, on March 8, 1994, the stress MUGA study was repeated, and his resting EF had increased from 14% to 54%, and with exercise (600 kg/min), the EF increased to 68%. On March 10, 1993, a repeat myocardial perfusion study during exercise was normal. Left ventricular dysfunction was no longer present. Fatigue disappeared, he resumed work as a millwright. At follow-up 2.5 years after treatment, the left ventricular function remained normal.

Discussion

This preliminary open trial of intravenous ganciclovir in patients with CFS, abnormal T-wave oscillations at Holter monitoring, and significant HCMV ELISA antibody titers was conducted to identify a possible subset of patients who may benefit from this therapy. A significant HCMV ELISA IgG antibody titer (> 120 U) with or without the presence of an HCMV ELISA IgG antibody titer, plus an absence of EBV VCA IgM antibody titer, along with an EBV EA antibody titer of <40 may help describe a CFS cohort of patients who may derive benefit from ganciclovir. This study was not blinded, randomized, or placebo-controlled, and the efficacy of ganciclovir has not been determined. The use of a single 30-day course of intravenous ganciclovir is arbitrary.

During the EBV infectious lytic cycle, antigen is expressed and can be divided into a diffuse (EA-D) complex and a cytoplasmic restricted (EA-R) complex. Here, we assayed EA-D [22]. The 52/50 kDa EA-D protein complex neutralizes EBV-encoded DNA polymerase activity. Elevated EBV VCA IgM and EBV EA antibody titers indicate recent EBV multiplication (e.g., within 90 days) [7,8,22]. Buffy coats from blood samples, urine samples, and cardiac biopsies did not contain infectious HCMV. It appears that we report a non-lytic, nonpermissive, persistent HCMV infection [24].

References

Ganciclovir in Chronic Fatigue


