Use of cytomegalovirus hyperimmunoglobulin for prevention of congenital cytomegalovirus disease: a retrospective analysis

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Abstract

Aims: The aim of this study was to investigate the current prenatal “off-label use” of cytomegalovirus hyperimmunoglobulin (CMV-HIG) in the prevention and treatment of congenital CMV (cCMV) infection, including the long-term outcome of the children.

Methods: This retrospective observational study comprised mothers and their children, born between January 1, 2006, and October 30, 2010. Prenatal CMV-HIG was administered after diagnosis of primary CMV infection of the mother. Clinical and virological data were collected from maternal and pediatric medical and laboratory reports. Follow-up was 12–36 months after birth.

Results: Forty-two women and 43 children met the study criteria. In total, 40 mothers and six unborn infants received 115 doses of CMV-HIG. The treatment group (TG; CMV-DNA polymerase chain reaction-positive amniotic fluid) included four mothers; the multinomial group (MG; CMV-positive mother and unknown CMV status of fetus) included 38 mothers (39 infants). For the four unborn infants in TG, CMV-HIG was administered either intraumbilically or into the amniotic fluid; three of the four mothers received intravenous CMV-HIG. Three children in TG remained CMV-positive and were asymptomatic at birth and during follow-up. One infant in TG had symptomatic cCMV infection in utero, at birth, and during follow-up. In MG, 37 of 38 women received intravenous CMV-HIG and two of 39 infants received CMV-HIG in utero. In total, 9 (23.1%) of 39 children in MG were positive for cCMV (including a terminated pregnancy). All eight instances of cCMV infection at birth in MG were asymptomatic at birth and during follow-up. The fetus from the terminated pregnancy showed no sonographic symptoms of cCMV infection. No severe side effect occurred in 115 CMV-HIG applications.

Conclusion: CMV-HIG was well tolerated. Compared with published untreated mother-child pairs, we observed a trend toward a smaller risk for intrauterine CMV transmission following CMV-HIG application. Signs of prenatal cCMV disease were not reversed after CMV-HIG.

Keywords: CMV hyperimmunoglobulin; congenital cytomegalovirus disease; congenital cytomegalovirus infection; cytomegalovirus; cytomegalovirus transmission; pregnancy; prevention; primary cytomegalovirus infection; treatment.

Introduction

Congenital cytomegalovirus (cCMV) infection is the most common cause of congenital disabilities and can cause auditory, cognitive, and neurological impairment in infants [3]. Administration of CMV hyperimmunoglobulin (CMV-HIG) to pregnant women who have a primary CMV infection has been reported to protect their unborn children against symptomatic cCMV infections [13]. At present, the only approved indication for CMV-HIG in Europe is for patients who have undergone solid organ transplantation. CMV-HIG is currently not approved for the prevention or therapy of cCMV infections; thus, its use in this indication constitutes so called “off-label use.” Given the sparsity of off-label use of CMV-HIG for treatment or prophylaxis of cCMV, this application has hardly been investigated. The aim of the present retrospective study is to assess the efficacy and safety of off-label use of CMV-HIG in the treatment and prophylaxis of cCMV infection.

Materials and methods

This retrospective observational study comprised women from Germany, Austria, Switzerland, and Belgium who received off-label CMV-HIG for prevention or treatment of intrauterine CMV infection.
after primary CMV infection and gave birth to their children between January 1, 2006, and October 30, 2010. All mother-child pairs whose medical records or laboratory reports related to their pregnancy were available were included. Gestational age (trimester) at the time of maternal infection was estimated from medical history, virology, and serology data. Laboratory diagnosis of the primary maternal CMV infection was established by detection of anti-CMV IgG seroconversion or low CMV IgG avidity in the presence of CMV IgM using commercial immunoassays. Written informed consent was obtained from all mothers or both parents. The study was approved by the Ethics Committee of the Johann Wolfgang Goethe-University Clinic, Frankfurt am Main (reference number 175/09). The primary outcome of the study was the incidence of cCMV infections. Secondary outcome parameters were whether the CMV-HIG administration was for prevention or therapy of cCMV infection, modes of CMV-HIG applications, CMV-HIG dosages, adverse events, outcome of the pregnancies, and follow-up results of the children.

If CMV was detected in the amniotic fluid, umbilical cord blood, blood, or urine of the neonate by polymerase chain reaction (PCR) or virus culture within 3 weeks after birth, cCMV infection was verified. The absence of intrauterine CMV infection was assessed by negative CMV culture or PCR in urine or blood from the neonate, taken within 3 weeks after birth. Statistical analyses were done descriptively.

**Results**

During the study period, 52 women were contacted. Ten mother-child pairs were not included because two women refused to participate in the study, three families did not return the informed consent form, two women were not treated with CMV-HIG, two women who received CMV-HIG had already been included in other clinical investigations, and one woman did not have a primary CMV infection. The remaining 42 women and their 43 infants met the study criteria and were included in the study (Figure 1).

In four pregnancies, CMV was detected in the amniotic fluid by PCR before the first dose of CMV-HIG. These pregnancies are summarized in the treatment group (TG).

In 36 pregnancies, no amniotic fluid testing of CMV was done before the first dose of CMV-HIG. In two cases, amniotic fluid before CMV-HIG was CMV-DNA negative, which does not definitively exclude prenatal CMV infection [5]. These 38 pregnancies formed the multinomial group (MG).

**Treatment Group**

There were four infants who received CMV-HIG prenatally for treatment of CMV infection (TG). Treatment with CMV-HIG (either intraumbilically or via amniotic fluid) was 16–35 days after diagnosis for the four unborn infants (Table 1). One infant received a total of three doses (900 U each), two infants received two doses (1000 U each), and one infant received two doses of 500 U each. In addition, three of the four mothers received intravenous treatment with CMV-HIG (Table 1).

The outcome for three of these infants was asymptomatic cCMV infection, and the outcome for the fourth infant was symptomatic cCMV infection (Tables 1 and 4).

For the four infants with cCMV disease before CMV-HIG application, it was not possible to determine whether the primary infection was before conception or during the first trimester (defined as “periconceptional” infection). CMV-
The positive CMV test was from amniotic fluid where a woman who had opted for termination of pregnancy at 23 weeks’ gestation. Of the positive CMV results in MG was from a woman who had primary infection during the second trimester (Table 3). One of the 37 mothers who received treatment with CMV-HIG, the time from diagnosis to the first treatment was up to 14 days for 16 (43.2%) mothers, 15–43 days for 14 (37.8%) mothers, and unknown for the remaining 7 (18.9%) mothers (Table 2).

Treatment with CMV-HIG was given to 2 (5.1%) of 39 unborn infants (via the umbilical vessel), with one of these two infants receiving an additional dose (intravenously) as a newborn.

In total, 9 (23.1%) of 39 children (95% confidence interval [CI], 9.5–37.9%) were positive for cCMV; the cCMV rate was 5 (20.8%) of 24 (95% CI, 3.3–38.4%) for those who had the primary infection during the first trimester or earlier and 4 (26.6%) of 15 (95% CI, 1.5–55.6%) for those who had the primary infection during the second trimester (Table 3). One of the positive CMV results in MG was from a woman who had opted for termination of pregnancy at 23 weeks’ gestation. The positive CMV test was from amniotic fluid (1.6×10⁶ copies/mL). The fetus had no abnormal findings on ultrasound. An autopsy was not performed.

All eight instances of cCMV infection in infants were asymptomatic (Table 4). During follow-up, none of the eight asymptomatic CMV-positive infants in MG received antiviral therapy after birth. For one of these children, lenticulostriate vasculopathy (week 2 and month 2) was observed during follow-up. The cerebrospinal fluid of this neonate was CMV-DNA negative, and the neurological examinations were normal. Another CMV-positive child in MG had a subependymal hemorrhage 2 days after birth, which resolved without untoward effects. No other clinically relevant findings were observed in these infants, with follow-up periods from 12 to 36 months. None of these children had a sensorineural hearing impairment at birth or during follow-up (Table 4).

**Adverse events**

In the entire study cohort, 40 mothers, five fetuses, and one newborn infant received a total of 115 doses of CMV-HIG (Tables 1 and 2). In the available medical reports, no adverse events were mentioned. In addition to the medical reports, all mothers were asked about adverse events due to therapy with CMV-HIG. It was well tolerated in all but two applications: one woman reported transient pain in her arm where CMV-HIG was given intravenously and one mother felt tired on the day of CMV-HIG administration. Accordingly, the rate of adverse events for applications was 2 (1.7%) of 115. No serious adverse event was reported.

**Discussion**

In our retrospective analysis concerning the current practice of CMV-HIG off-label use, we assessed two main indications: the application of CMV-HIG in pregnancies with confirmed intrauterine CMV infection (TG) and in pregnancies complicated by primary CMV infection where the CMV status of the fetus was unknown or unresolved (MG).

**Treatment group**

In TG, three of the four CMV-positive mothers gave birth to infants with asymptomatic cCMV. For the unborn child who had previously demonstrated a CMV infection with typical sonomorphological symptoms in utero, the CMV-HIG administration showed no obvious benefit and the child had a clinically symptomatic cCMV infection at birth. Two single
Table 2  Estimated time of CMV infection, administration of CMV-HIG, and outcome in MG.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Estimated time of CMV infection</th>
<th>From diagnosis to treatment (days)</th>
<th>Route of CMV-HIG administration</th>
<th>Freq</th>
<th>Dos/kg (U)</th>
<th>Dos/ad (U)</th>
<th>Outcome child (cCMV infection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN 1</td>
<td>First trimester</td>
<td>17</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>13,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>AN 2</td>
<td>First trimester</td>
<td>38</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Not infected</td>
</tr>
<tr>
<td>AS 3</td>
<td>Periconceptional</td>
<td>n.a.</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Not infected</td>
</tr>
<tr>
<td>AB 4</td>
<td>Second trimester</td>
<td>15</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>200</td>
<td>17,000</td>
<td>Asymptomatic infected</td>
</tr>
<tr>
<td>BA 5</td>
<td>Second trimester</td>
<td>n.a.</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>12,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>BK 8</td>
<td>Periconceptional</td>
<td>40</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>15,000</td>
<td>Induced abortion</td>
</tr>
<tr>
<td>DD 9</td>
<td>Second trimester</td>
<td>10</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>270</td>
<td>15,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>ES 10</td>
<td>Periconceptional</td>
<td>n.a.</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>200</td>
<td>16,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>EA 11</td>
<td>Second trimester</td>
<td>16</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>15,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>FS 12</td>
<td>Second trimester</td>
<td>12</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>13,000</td>
<td>Asymptomatic infected</td>
</tr>
<tr>
<td>GS 13</td>
<td>First trimester</td>
<td>29</td>
<td>Intravenous to mother</td>
<td>1×</td>
<td>200</td>
<td>15,000</td>
<td>Asymptomatic infected</td>
</tr>
<tr>
<td>HS 14</td>
<td>First trimester</td>
<td>41</td>
<td>Intravenous to mother</td>
<td>5×</td>
<td>200</td>
<td>15,000</td>
<td>Asymptomatic infected</td>
</tr>
<tr>
<td>JA 15</td>
<td>First trimester</td>
<td>n.a.</td>
<td>Intraumbilical</td>
<td>2×</td>
<td>n.a.</td>
<td>500</td>
<td>Not infected</td>
</tr>
<tr>
<td>JS 16</td>
<td>First trimester</td>
<td>n.a.</td>
<td>Intraumbilical</td>
<td>3×</td>
<td>n.a.</td>
<td>800</td>
<td>Not infected</td>
</tr>
<tr>
<td>KT 17</td>
<td>Second trimester</td>
<td>13</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>200</td>
<td>15,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>KA 18</td>
<td>Periconceptional</td>
<td>15</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>18,000</td>
<td>Asymptomatic infected</td>
</tr>
<tr>
<td>KS 19</td>
<td>First trimester</td>
<td>41</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Not infected</td>
</tr>
<tr>
<td>KB 20</td>
<td>Periconceptional</td>
<td>31</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>200</td>
<td>15,000</td>
<td>Asymptomatic infected</td>
</tr>
<tr>
<td>LM 21</td>
<td>Periconceptional</td>
<td>43</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Not infected</td>
</tr>
<tr>
<td>LA 23</td>
<td>Second trimester</td>
<td>14</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>15,000</td>
<td>Asymptomatic infected</td>
</tr>
<tr>
<td>LS 24</td>
<td>First trimester</td>
<td>11</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>200</td>
<td>10,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>OA 25</td>
<td>Periconceptional</td>
<td>n.a.</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>15,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>PA 26</td>
<td>First trimester</td>
<td>17</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>14,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>RC 28</td>
<td>First trimester</td>
<td>17</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>200</td>
<td>13,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>RS 29</td>
<td>First trimester</td>
<td>6</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Not infected</td>
</tr>
<tr>
<td>SP 30</td>
<td>Second trimester</td>
<td>7</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>n.a.</td>
<td>n.a.</td>
<td>1× Asymptomatic infected</td>
</tr>
<tr>
<td>ST 32</td>
<td>Second trimester</td>
<td>11</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>200</td>
<td>14,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>SI 33</td>
<td>Second trimester</td>
<td>9</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Not infected</td>
</tr>
<tr>
<td>SK 34</td>
<td>First trimester</td>
<td>n.a.</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>100</td>
<td>6000</td>
<td>Not infected</td>
</tr>
<tr>
<td>SP 35</td>
<td>Second trimester</td>
<td>11</td>
<td>Intravenous to mother</td>
<td>1×</td>
<td>100</td>
<td>15,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>SM 36</td>
<td>Second trimester</td>
<td>8</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>18,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>SK 37</td>
<td>Second trimester</td>
<td>11</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Not infected</td>
</tr>
<tr>
<td>SS 38</td>
<td>First trimester</td>
<td>7</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>13,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>TP 39</td>
<td>First trimester</td>
<td>6</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Not infected</td>
</tr>
<tr>
<td>VC 40</td>
<td>Periconceptional</td>
<td>15</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>200</td>
<td>15,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>WS 41</td>
<td>First trimester</td>
<td>9</td>
<td>Intravenous to mother</td>
<td>3×</td>
<td>200</td>
<td>12,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>WS 42</td>
<td>Second trimester</td>
<td>1</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>200</td>
<td>18,000</td>
<td>Not infected</td>
</tr>
<tr>
<td>BS 43</td>
<td>Periconceptional</td>
<td>n.a.</td>
<td>Intravenous to mother</td>
<td>2×</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Not infected</td>
</tr>
</tbody>
</table>

Freq=Frequency, Dos/kg=Dosage per kg body weight, Dos/ad=Dosage per administration, U=Units of the reference preparation at the Paul-Ehrlich-Institute, Frankfurt/M. (Germany), n.a.=not available.

Table 3  Incidence of cCMV infections in MG in relation to the estimated time of maternal primary CMV infection.

<table>
<thead>
<tr>
<th>Estimated time of primary CMV infection</th>
<th>Number of mothers (n)</th>
<th>Number of children (n)</th>
<th>Number of cCMV-infected children (n)</th>
<th>Rate of cCMV-infected children (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periconceptional/first trimester</td>
<td>24</td>
<td>24</td>
<td>5</td>
<td>20.8 (3.3–38.4)</td>
</tr>
<tr>
<td>Second trimester</td>
<td>14</td>
<td>15</td>
<td>4</td>
<td>26.6 (1.5–55.6)</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>39</td>
<td>9</td>
<td>23.1 (9.5–37.9)</td>
</tr>
</tbody>
</table>
Table 4  Diagnostic at birth and follow-up investigations of the cCMV-infected children.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>TG</th>
<th>MG</th>
</tr>
</thead>
<tbody>
<tr>
<td>BJ 7</td>
<td>w1: U-PCR +</td>
<td>w1: U-PCR +</td>
</tr>
<tr>
<td>BJ 32</td>
<td>w1: B-PCR +</td>
<td>w1: B-PCR +</td>
</tr>
<tr>
<td>LF 22</td>
<td>m4: U-PCR +</td>
<td>m4: U-PCR +</td>
</tr>
<tr>
<td>PJ 27</td>
<td>m5: U-PCR –</td>
<td>m5: U-PCR +</td>
</tr>
</tbody>
</table>

CMV diagnostic
- d1: U-PCR +
- w1: U-PCR +
- w1: B-PCR +
- d4: B-PCR +
- m5: U-PCR +
- m5: U-PCR –

Antiviral therapy: No
Full blood count:
- d2: NAD
- m6: NAD
- m12: NAD
- m24: NAD

Liver function test:
- d2: NAD
- w1: NAD
- m4: NAD
- w1: NAD

Physical examination:
- d1: Pathologic; microcephalia
- d1: Pathologic; microcephalia
- d1: Pathologic; microcephalia
- d1: Pathologic; microcephalia
- m2: NAD
- m2: NAD
- m2: NAD
- m2: NAD

Neuroimaging (US):
- m36: NAD
- m24: NAD
- m36: NAD
- m24: NAD
- m36: NAD
- m24: NAD
- m36: NAD
- m24: NAD

- w1: Small cyst subependymal
- w1: Calcification, cerebellar cyst
- w1: NAD
- w1: NAD
- w1: NAD
- w1: NAD
- w1: NAD
- w3: LSV

Body position slight asymmetry
- m12: NAD
- m24: NAD
- m36: NAD
- m24: NAD
- m36: NAD
- m24: NAD
- m36: NAD
- m24: NAD

Calcification, cerebellar cyst
doses of CMV-HIG were given in this case: 500 U into the amniotic fluid and 500 U into the umbilical vein. In contrast to our findings, reversal of clinically relevant CMV-related symptoms in utero with CMV-HIG administration has been reported in published literature. Breinl and Lassmann [2] in 1989 reported regression of a CMV-associated hydrops fetalis after two intravenous doses of CMV-HIG to the mother. In another study reported by Nigro et al. [14], regression of CMV-associated symptoms was reported for three unborn infants after repeated intravenous doses of CMV-HIG to the mothers and once into the amniotic fluid of each fetus. In these successful four cases, CMV-HIG was given intravenously to the mother, whereas the pregnant woman in our cohort did not receive intravenous CMV-HIG.

The other three infants of TG had no cCMV-related sonographic symptoms in utero. In this cohort, both the mothers and the unborn infants received treatment with CMV-HIG. The babies were born with asymptomatic cCMV infection and remained asymptomatic during the follow-up examinations of 12 or more months. Dollard et al. [4] in 2007 and Foulon et al. [8] in 2010 reported that 13.5–21.5 % of all untreated infants with asymptomatic cCMV infection at birth will develop sequelae later in life. None of the asymptomatically cCMV-infected children in our study cohort developed sequelae during the follow-up. Unfortunately, our study cohort is too small to determine a significant difference between our CMV-HIG-treated mother-child pairs and the untreated cohorts reported in the literature.

**Multinomial group**

In MG, the overall incidence of cCMV infections was 23.1 % (95% CI, 9.5–37.9 %). Two recent studies investigated pregnant women with primary CMV infection who did not receive CMV-HIG. Intrauterine CMV transmission was reported for 250 (46.6 %) of 537 women (95% CI, 42.3–50.9 %) in the study published by Bodéus et al. in 2010 [1] and for 94 (37.9 %) of 248 women (95% CI, 31.8–44.3 %) in the study reported by Enders et al. [6] in 2011.

According to the estimated time of maternal infection, we found a CMV transmission rate after CMV-HIG treatment of 20.8 % (95% CI, 1.5–55.6 %) following periconceptional or first-trimester infection and 26.6 % (95% CI, 1.5–55.6 %) after the second-trimester CMV infection. Without CMV-HIG treatment, Bodéus et al. [1] reported transmission rates of 34.5 % (95% CI, 25.8–44.0 %) and 44.1 % (95% CI, 35.6–52.9 %) and Enders et al. [6] of 30.1 % (95% CI, 20.5–41.2 %) and of 38.2 % (95% CI, 27.3–50.0 %) after first- and second-trimester CMV infections, respectively. Regarding these findings, we observed a trend toward lower intrauterine transmission rates following CMV-HIG treatment of pregnant women with confirmed primary CMV infection during and before the second trimester.

In MG, all infants with cCMV infection were clinically asymptomatic at birth and remained asymptomatic during the follow-up. With regard to the reported prevalence for symptomatic cCMV-infected children of 11 % [11], the absence of symptomatic cCMV in our study is promising; however,
our study population is too small to assess whether there is a clinically meaningful benefit for CMV-HIG application in this population.

A small study reported by Foulon et al. [7] in 2008 related sensorineural hearing impairment in cCMV-infected children to the trimester of maternal primary CMV infection. They found 4 (80%) of five cCMV-infected children with hearing impairment in the group of mothers with primary CMV infection in the first trimester. In our MG, four mothers with primary CMV infection periconceptional or in the first trimester gave birth to four children with asymptomatic cCMV infection. Not one of them had a persistent sensorineural hearing impairment at birth or during the follow-up. Again, our number of investigated children is small, but the difference between no hearing loss after CMV-HIG treatment and 80% hearing loss without CMV-HIG treatment after maternal primary HCMV infection in the first trimester shows a tendency to a benefit with CMV-HIG treatment.

Doses, routes and frequency of CMV-HIG application

With regard to the doses, routes, and frequency of administration of CMV-HIG, we found a wide range used by the different gynecologists of the overall study group (Tables 1 and 2). In MG, the median CMV-HIG dosage was 200 U/kg body weight intravenously and the majority of women received two doses or more. Nigro et al. [13] published the largest cohort of CMV-HIG-treated pregnant women to date. In this study’s TG (CMV-positive amniotic fluid), CMV-HIG was administered once to the mother at an intravenous dose of 200 U/kg and additionally 400 U/kg fetal weight into the amniotic fluid or into the umbilical cord in the event of ultrasonographic evidence of persistent fetal involvement. In the prevention group of this study (CMV status of the amniotic fluid not known), CMV-HIG was intravenously given at a dose of 100 U/kg body weight to the mother every month until delivery.

At present, CMV-HIG is not approved for prevention of cCMV infection for CMV-seroconverted pregnant women. Based on current published data, the prenatal application of CMV-HIG in pregnancies with proven primary CMV infection cannot be recommended with evidence-based background [12]. Prospective randomized trials investigating the efficacy of CMV-HIG in the prevention of cCMV infection with definitive therapeutic regimes are already running [9, 15], but the data are not published yet. This obviously leads to a wide range of doses, routes, and frequency of administration of CMV-HIG that are currently used by gynecologists, as shown in this retrospective analysis.

Adverse events

No serious adverse event for CMV-HIG was reported. One instance of fatigue and one of pain at the injection site were reported as adverse events. Accordingly, the adverse event rate in our study is low (1.7%). Nigro et al. [13] found no adverse event after CMV-HIG application in their study.

Examinations of neonates with cCMV infection

According to the diagnostic tests at birth and follow-up examinations of the cCMV-infected children, we found a high variation both with regard to the frequency and the type of the examinations performed in our study cohort (Table 4). None of the cCMV-infected children in our cohort was investigated as suggested in the follow-up recommendations for cCMV-infected children published by Gandhi et al. [10]. There is an obvious difference between the more comprehensive diagnostic efforts in children with prenatal diagnosis of cCMV (TG) and postnatal diagnosis of cCMV (MG).

Limitations of the study

Limitations of this study are the retrospective design, lack of a control group, and the heterogeneity of the available data.

Conclusion

This is the first study investigating the current off-label use of CMV-HIG during pregnancy in Europe. Our results show the current varied use of CMV-HIG in the context of prevention and prenatal treatment of cCMV infection. Administration of CMV-HIG after primary maternal CMV infection was well tolerated. Compared with untreated mother-child pairs reported in the literature, we observed a trend toward a smaller risk for intrauterine CMV transmission and symptomatic cCMV infection following CMV-HIG administration. Thus, application of CMV-HIG in our cohort did not cause harm and seems to carry a benefit in the prevention of cCMV infection.

Symptoms of prenatal cCMV disease persisted after CMV-HIG. Prospective randomized trials on the use of CMV-HIG under standardized regimens with respect to dosage, mode, and time of administration are urgently needed to obtain better efficacy and safety data on CMV-HIG for the prevention and prenatal treatment of cCMV infection.

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