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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

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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 three asymptomatic cCMV infections, CMV was first diagnosed during the first trimester for two infants and during the second trimester for one infant. For all three infants, CMV-HIG was administered to both the unborn child and the mother. At the age of 1 year, medical examinations done by their local pediatrician were found to be normal. No antiviral therapy was given after birth, and none of the three infants developed clinical symptoms related to their cCMV infection (Table 4).

For the infant in TG 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-

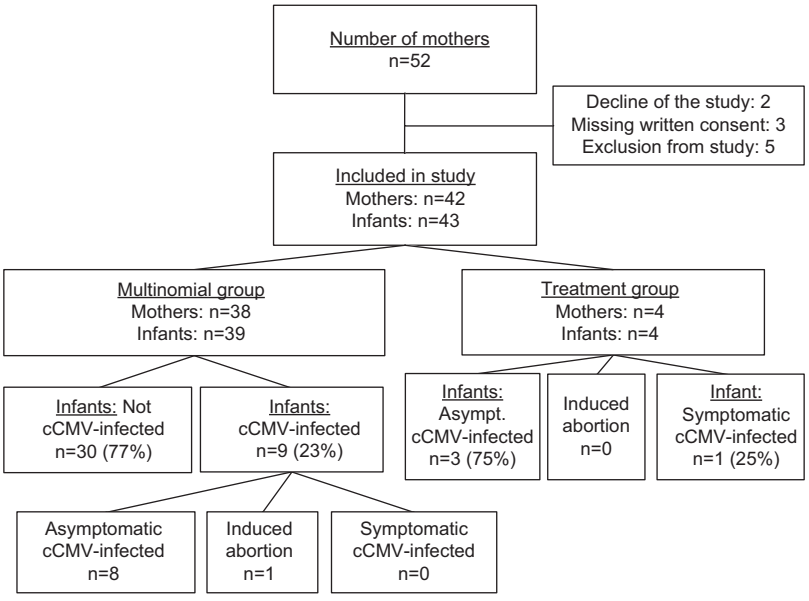

Figure 1 Study population.

Table 1 Estimated time of CMV infection, administration of CMV-HIG, and outcome in TG.

Patient ID	Estimated time of CMV infection	From diagnosis to treatment (days)	Route of CMV-HIG administration	Freq	Dos/kg (U)	Dos/ad (U)	Outcome child (cCMV infection)
BM 7	First trimester	21	Intravenous to mother	1×	220	15,000	Asymptomatic
			Intraumbilical	3×		900	infected
SC 31	First trimester	35	Intravenous to mother	2×	200	15,000	Asymptomatic
			Amniotic fluid	2×		1000	infected
LC 22	Second trimester	21	Intravenous to mother	3×	180	15,000	Asymptomatic
			Amniotic fluid	2×		1000	infected
PA 27	Periconceptional	16	Amniotic fluid	1×		500	Symptomatic
			Intraumbilical	1×		500	infected

Freq=Frequency, Dos/kg=Dosage per kilogram body weight, Dos/ad=Dosage per administration, U=Units of the reference preparation at the Paul-Ehrlich-Institute, Frankfurt/Maim (Germany).

HIG was administered to the unborn child intraumbilically and through amniotic fluid (at doses of 500 U). The mother was not treated with CMV-HIG. Before the first application of CMV-HIG, the fetus had shown abnormal ultrasound findings, namely intrauterine growth retardation, microcephalia, and hyperechogenic bowl. The child was born with symptomatic cCMV infection and was treated with ganciclovir and valganciclovir. The child remained microcephalic and had impaired mental and motor skills, vision, and hearing.

Multinomial group

MG included 38 women and their 39 infants. CMV-HIG was administered to 37 mothers and to two unborn children (Table 2).

The 37 mothers received a total of 91 intravenous doses at a median dose of 200 U/kg body weight (Table 2). The diagnosis of the primary CMV infection was during the first trimester or earlier for 24 (63.2%) of 38 mothers and during the second trimester for 14 (36.8%) of 38 mothers; there was no diagnosis during the third trimester. For 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 (1.6×10^6 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.

Patient ID	Estimated time of CMV infection	From diagnosis to treatment (days)	Route of CMV-HIG administration	Freq	Dos/kg (U)	Dos/ad (U)	Outcome child (cCMV infection)
AN 1	First trimester	17	Intravenous to mother	2×	200	13,000	Not infected
AN 2	First trimester	38	Intravenous to mother	2×	n.a.	n.a.	Not infected
AS 3	Periconceptional	n.a.	Intravenous to mother	3×	n.a.	n.a.	Not infected
AB 4	Second trimester	15	Intravenous to mother	3×	200	17,000	Asymptomatic infected
BA 5	Second trimester	n.a.	Intravenous to mother	2×	200	12,000	Not infected
				2×	100	6000	
BK 8	Periconceptional	40	Intravenous to mother	2×	200	15,000	Induced abortion
DD 9	Second trimester	10	Intravenous to mother	3×	270	15,000	Not infected
ES 10	Periconceptional	n.a.	Intravenous to mother	3×	200	16,000	Not infected
EA 11	Second trimester	16	Intravenous to mother	2×	200	15,000	Not infected
FS 12	Second trimester	12	Intravenous to mother	2×	200	13,000	Asymptomatic infected
GS 13	First trimester	29	Intravenous to mother	1×	200	15,000	Asymptomatic infected
HS 14	First trimester	41	Intravenous to mother	5×	200	15,000	Asymptomatic infected
			Intravenous to mother	1×	100		
JA 15	First trimester	n.a.	Intraumbilical	2×	n.a.	500	Not infected
			Intraumbilical	3×	n.a	800	
			Intravenous to newborn	1×	50	150	
JS 16	First trimester	n.a.	Intravenous to mother	3×	n.a.	n.a.	Not infected
KT 17	Second trimester	13	Intravenous to mother	2×	200	15,000	Not infected
KA 18	Periconceptional	15	Intravenous to mother	2×	200	18,000	Asymptomatic infected
KS 19	First trimester	41	Intravenous to mother	2×	n.a.	n.a.	Not infected
KB 20	Periconceptional	31	Intravenous to mother	3×	200	15,000	Asymptomatic infected
LM 21	Periconceptional	43	Intravenous to mother	2×	n.a.	n.a.	Not infected
LA 23	Second trimester	14	Intravenous to mother	2×	200	15,000	Asymptomatic infected
LS 24	First trimester	11	Intravenous to mother	3×	200	10,000	Not infected
OA 25	Periconceptional	n.a.	Intravenous to mother	2×	200	15,000	Not infected
PA 26	First trimester	17	Intravenous to mother	2×	200	14,000	Not infected
RC 28	First trimester	17	Intravenous to mother	3×	200	13,000	Not infected
RS 29	First trimester	6	Intravenous to mother	2×	n.a.	n.a.	Not infected
SP 30	Second trimester	7	Intravenous to mother	2×	n.a.	n.a.	1× Asymptomatic infected 1× Not infected
ST 32	Second trimester	11	Intravenous to mother	3×	200	14,000	Not infected
SI 33	Second trimester	9	Intravenous to mother	2×	n.a.	n.a.	Not infected
SK 34	First trimester	n.a.	Intravenous to mother	3×	100	6000	Not infected
SP 35	Second trimester	11	Intravenous to mother	1×	100	15,000	Not infected
SM 36	Second trimester	8	Intravenous to mother	2×	200	18,000	Not infected
			Intraumbilical	4×	n.a.	800	
SK 37	Second trimester	11	Intravenous to mother	2×	n.a.	n.a.	Not infected
SS 38	First trimester	7	Intravenous to mother	2×	200	13,000	Not infected
TP 39	First trimester	6	Intravenous to mother	2×	n.a.	n.a.	Not infected
VC 40	Periconceptional	15	Intravenous to mother	3×	200	15,000	Not infected
WS 41	First trimester	9	Intravenous to mother	3×	200	12,000	Not infected
WS 42	Second trimester	1	Intravenous to mother	2×	200	18,000	Not infected
WS 43	Periconceptional	n.a.	Intravenous to mother	2×	n.a.	n.a.	Not infected

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.

Estimated time of primary CMV infection	Number of mothers (n)	Number of children (n)	Number of cCMV-infected children (n)	Rate of cCMV-infected children (%) (95% CI)
Periconceptional/first trimester	24	24	5	20.8 (3.3–38.4)
Second trimester	14	15	4	26.6 (1.5–55.6)
Total	38	39	9	23.1 (9.5–37.9)

Table 4 Diagnostic at birth and follow-up investigations of the cCMV-infected children.

	TG				MG							
Patient ID	BJ 7	BJ 32	LF 22	PJ 27	AM 4	FM 12	GH 13	TF 14	KC 18	KJ 20	LM 23	SL 31
CMV diagnostic	d1: U-PCR +	w1: U-PCR +	w1: U-PCR +	w1: U-PCR +	w1: U-PCR +	w1: U-PCR +	w1: U-PCR +	w1: U-PCR +	AF: PCR +	w1: U-PCR +	d3: U-PCR +	w1: U-PCR +
	d1: B-PCR +	w1: B-PCR +	w1: B-PCR +	w1: B-PCR +	w1: B-PCR +	w1: B-PCR +		w1: B-PCR +		w1: B-PCR +	m2: U-PCR +	
	d4: CSF-PCR –			m4: U-PCR +	m4: B-PCR +			w1: T-PCR +		w3: B-PCR +	m2: B-PCR –	
	m5: U-PCR +			m5: U-PCR –	m4: U-PCR +					m2: CSF-PCR–	m6: U-PCR +	
										m2: B-PCR +/–		
Antiviral therapy	No	No	No	Yes	No	No	No	No	No	No	No	No
Full blood count	d2: NAD	w1: NAD	w1: NAD	w1: Anemia, thrombopenia		d1: NAD		m6: NAD		w3: NAD	m2: NAD	
										m2: NAD	m6: NAD	
				m4: NAD								
Liver function test	d2: NAD	w1: NAD	w1: NAD	w1: NAD						m2: AST +	m2: NAD	
											m6: NAD	
Physical examination	d1: NAD	d1: NAD	d1: NAD	d1: Pathologic; microcephalia	d1: NAD	d1: NAD	m1: NAD	d1: NAD	d1: NAD	d1: NAD	d1: NAD	d1: NAD
	d7: NAD	d5: NAD	d3: NAD		d7: NAD	d10: NAD	m2: NAD	d6: NAD	d3: NAD	d3: NAD	d4: NAD	d7: NAD
	w4: NAD	w4: NAD	w4: NAD	w6: Pathologic	w3: NAD	w4: NAD	m4: NAD	w4: NAD	m1: NAD	w3: NAD	w4: NAD	w4: NAD
	m3: NAD	m3: NAD	m3: NAD	m6: Pathologic	m4: NAD	m4: NAD	m6: NAD	m4: NAD	m3: NAD	w6: NAD	m2: NAD	m3: NAD
	m6: NAD	m6: NAD	m6: NAD	m9: Pathologic	m7: NAD	m6: NAD	m12: NAD	m6: NAD	m6: NAD	m2: NAD	m6: NAD	m6: NAD
	m12: NAD	m12: NAD	m12: NAD	m12: Pathologic	m12: NAD	m12: NAD	m18: NAD	m12: NAD	m12: NAD	m3: Body position slight asymmetry	m12: NAD	m12: NAD
	m24: NAD		m24: NAD	m20: Pathologic; severe retardation		m24: NAD		m24: NAD		m8: NAD		
	m36: NAD							m36: NAD		m12: NAD		
Neuroimaging (US)	w1: NAD	w1: NAD	w1: Small cyst sub-ependymal	w1: Calcification, cerebellar cyst		w1: NAD	w1: NAD	w1: NAD		w3: LSV	w1: NAD	d2: IVH I° R
										m2: LSV	m2: NAD	m3: NAD m10: NAD

(Table 4 continued)

	TG				MG							
Patient ID	BJ 7	BJ 32	LF 22	PJ 27	AM 4	FM 12	GH 13	TF 14	KC 18	KJ 20	LM 23	SL 31
Ophthalmology screen	d4: NAD	w1: NAD	w1: NAD	m1: Retina scar		w1: NAD		w1: Little bleeding; no retinitis	7m: VEP normal	m1: NAD	m1: NAD	d3: NAD
			m23: NAD							m6: Right hyperopia; no retinitis m12: Unvaried		m14: NAD
Hearing assessment	w1: NAD	w1: NAD	w1: NAD	m1: pathologic	w1: NAD	w1: NAD	m2: NAD	w1: NAD	w1: NAD	d3: NAD	w1: refer L	d3: NAD
	m6: NAD	m6: NAD	w4: NAD	m12: Pathologic	m18: NAD	m6: NAD	m5: NAD	m3: NAD	m10: NAD	w6: NAD	m3: NAD	m14: NAD
	m36: NAD	m19: NAD	m3: NAD			m12: NAD	m12: NAD	m6: refer L		m5: NAD	m10: NAD	
		m30: NAD	m20: NAD				m24: NAD	m14: NAD		m8: NAD		
										m13: NAD		

AF=Amniotic fluid, AST=Aspartate aminotransferase, B=Blood, +/−=borderline, +=positive, −=positive, CSF=Cerebrospinal fluid, IVH=Intraventricular hemorrhage, L=left, LSV=Lenticulostriatal vasculopathy, m=month, NAD=no abnormality detected, T=Throat, U=Urine, VEP=visual evoked potentials, d=day, w=week, US=ultrasound.

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 sequela later in life. None of the asymptomatically cCMV-infected children in our study cohort developed sequela 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, 3.3–38.4%) 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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