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SHORT REPORT

Combined treatment with immunoglobulin and valaciclovir in pregnant women with cytomegalovirus infection and high risk of symptomatic fetal disease

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ABSTRACT

Introduction: Congenital cytomegalovirus (CMV) infection is one of the most common during pregnancy. The infection, particularly in the first trimester, is associated with important sequelae in up to half of the children. Valaciclovir and immunoglobulin have been tested separately for the treatment of fetal CMV infection with relative success. Nevertheless, there is no experience with the simultaneous use of both therapies.

Methods: combination therapy (oral valaciclovir 2 g/6h until the end of pregnancy and intravenous hyperimmune gamma globulin 200 UI/kg) was offered to pregnant women with CMV infection acquired during pregnancy and viral load (VL) in amniotic fluid above 10^5 copies/ml and/or brain injuries in the ultrasonography. Additional immunoglobulin monthly doses were used in case of ultrasonography or MRI evidence of persistent fetal involvement. Neurological and hearing evaluations of infants were performed at birth and every 3 months during follow-up.

Results: 15 pregnant women were enrolled: primary infection, 14, non-primary infection, 1; first trimester, 11, second trimester, 4. Mean gestational age at the start of combination treatment were 23.2 weeks and 29.3 weeks, depending on the infection being diagnosed in the first or the second trimester, respectively. Median VL of CMV-DNA in amniotic fluid was 62.5×10^5 copies/ml. Intrauterine progression of fetal brain lesions was only observed in two cases in which the dose of CMV-HIG was repeated, slowing their progression. Although the treatment has failed to reverse ultrasound fetal lesions, only 3 children were born with hearing impairment and their psychomotor development was consistent with chronological age in all patients but one. Combination therapy was not associated with adverse effects in either the mothers or the fetuses.

Conclusion: Combination therapy with immunoglobulin and valaciclovir may be a useful alternative in CMV fetal infection, particularly if changes in cerebral echography or high VL in the amniotic fluid are present.

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Introduction

Congenital cytomegalovirus (CMV) infection is a relatively common intrauterine infection occurring in approximately 0.6% of all newborns. Infection rates are higher in areas with high rates of maternal seroprevalence in primary infection and with increasing gestational age [1].

Ten to fifteen percent of children show symptoms at birth, and about half have permanent sequelae, including sensorineural hearing loss, cognitive deficits, ophthalmologic abnormalities and motor defects [2]. Sequelae may also appear later in 7–10% of asymptomatic newborns [1,2]. A high viral load (VL) in the amniotic fluid ($>10^5$ copies/ml) and infection in the first trimester have been associated with a higher risk of symptomatic fetal infection [2,3].

Diagnosed fetal infections have two therapeutic options: hyperimmune gamma globulin and valaciclovir. Cytomegalovirus hyperimmune globulin (CMV-HIG) is thought to act by inhibiting both the direct and indirect effects of CMV infection, *via* modulation of the innate and adaptive immune responses. CMV-HIG therapy was associated with lower rates of congenital disease [4], lower incidence of long-term sequelae [5],

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and even the regression of some fetal abnormalities [4,6,7].

On its turn, oral valaciclovir decreased CMV VL and produced therapeutic concentrations in the blood of infected fetuses [8], leading to improved outcome of fetuses with extra-cerebral or mild cerebral ultrasound changes [9]. Despite valaciclovir and CMV-HIG efficacy as monotherapies, there is no experience in their combined use.

Methods

From April 2017 to August 2019 combination therapy was offered to pregnant women with CMV infection acquired during pregnancy (defined as IgG seroconversion, IgM + and IgG + with low avidity or IgM + and IgG + with high avidity and positive viremia or viruria) and VL in amniotic fluid above 10^5 copies/ml and/or brain injuries in the ultrasonography. All pregnant women wanted to continue with the pregnancy, despite knowing the risks associated with CMV infection, and signed an informed consent. Approval from the Ethic Committee HULP PI-1492 is awaited.

Ultrasound scans were carried out by experienced examiners (Voluson E8, GE, Kretz, Zipf, Austria). Magnetic resonance imaging (MRI) was performed at 28–32 weeks (1.5 T GE Sigma Horizon, Echo speed, LX MRI scanner, Milwaukee, WI, USA).

Combination therapy consisted of oral administration of valaciclovir 2 g/6h until the end of pregnancy and of intravenous CMV-HIG (200 UI/kg). Additional monthly doses were used in case of ultrasonography or MRI evidence of persistent fetal involvement. Neurological and hearing evaluations of infants were performed at birth and every 3 months during follow-up. Adverse effects of medication were monitored one week after starting treatment and every 3 weeks at each control visit afterwards.

Results

Fifteen pregnant women were enrolled: primary infection, 14; non-primary infection, 1; first trimester, 11, second trimester, 4. Mean gestational age at CMV infection diagnosis was 9.5 weeks and 24.6 weeks, and amniocentesis was performed between weeks 20 and 21 or 26 and 29, according to the diagnosis being done in the first or second trimester, respectively. Median VL of CMV-DNA in amniotic fluid was 62.5×10^5 copies/ml (IQR = $30.8–100 \times 10^5$).

Mean gestational age at the start of combination treatment was 23.2 weeks when fetal infection was diagnosed in the first trimester, and 29.3 weeks, when it was diagnosed in the second trimester. Therapy was well-tolerated and no significant adverse effects were documented (two cases of transient epigastralgia and one of mild headache, both related to valaciclovir only).

In one pregnant woman ultrasound findings were already present prior to maternal seroconversion, which occurred in the second trimester and, consequently, not attributable to CMV infection. Actually, the first amniocentesis was negative for CMV. Amniocentesis was repeated later (week 29) and a high VL (1.8×10^5 copies/ml) was detected, which is the reason why combination therapy was offered (case 11).

Of the remaining 14 pregnant women, eight presented abnormal ultrasound or neuroimaging findings. In three cases the immunoglobulin cycle was repeated because of the persistence of fetal brain injuries. In two women CMV-HIG was repeated due to aggravation of the brain damage and was able to stop the progression. In the other six women, imaging studies were normal during the whole pregnancy (Table 1).

All pregnant women gave birth to full-term, normal weight, newborns (except one preterm rupture of membranes, 35 + 3 weeks, and 2 children with weight < P10). Nine neonatal imaging tests confirmed prenatal findings. Three newborns without prenatal imaging abnormalities showed mild findings in the postnatal period (Table 1).

All newborns but one had normal blood tests and physical exams, including neurological examination. One of the infections occurred in the first trimester but was not diagnosed until the third, following the ultrasound findings. In this case, the pregnant woman received the first dose of combination therapy at 34 weeks. This newborn was preterm, not small for gestational age (weight 2.130 g), had hepatomegaly and purpura, abnormal neurological examination, thrombocytopenia, hypertransaminasemia and hyperbilirubinemia at birth (case 14).

All newborns received antiviral treatment except one, who presented normal prenatal imaging tests and was asymptomatic at birth. Of the remaining 14 infants, 13 received treatment with oral valganciclovir and 1 with intravenous ganciclovir (case 14). One patient continued follow up in another center, 4 infants were still under treatment when this paper was written (cases 12, 13, 14, 15), and 5 asymptomatic cases maintained treatment until a normal MRI result. In all other cases treatment was maintained for 6 months. All presented normal psychomotor

Table 1. Clinical and analytical characteristics of pregnant women infected with cytomegalovirus and their offspring after immunoglobulin and valaciclovir combined therapy during pregnancy.

Case	Seroconversion (weeks + days of gestation)	Prenatal ultrasound	Fetal brain MRI	Amniocentesis (weeks + days of gestation: VL in $\times 10^5$copies/ml)	Gama globulin doses (200 UI/kg)	VL in blood/urine ($\times 10^3$copies/ml)	Neonatal brain MRI	Auditory /ophthalmological/ psychomotor development abnormalities at birth	Auditory /ophthalmological /psychomotor development abnormalities (12 months)
1	Primary infection 2T (22 + 1)	Normal	Normal	26 + 3: 56	1	U: 40,291	Germline cysts	NO	Lost to follow up
2	Non-primary infection 1T (9 + 3)	Mild ventriculomegaly	Vetriculomegaly	21 + 4: 21.4	2	B: 7.13 U: 2.64	Ventriculomegaly Periventricular cysts	NO	NO
3	Primary infection 1T (8 + 5)	Heterogeneous echotexture of the right caudate nucleus Right hypoechoic image in right temporal lobe	Right temporal subcortical cyst	21 + 1: 98.2	1	B: 1.58 U: 22,900	Normal	NO	NO
4	Primary infection 1T (9 + 1)	Hyperintense intestines Cysts in temporal lobes	Cysts in temporal lobes	21: 35	2	B: 18.7 U: 346,000	Temporal, frontal and parietal hyperintensity	Moderate-severe hearing loss in left ear	Punctate cataract in right eye Moderate-severe hearing loss in left ear
5	Primary infection 1T (10 + 2)	Ventriculomegaly Synechiae	Ventriculomegaly Synechiae	21 + 2: 100	3	B: 3.54 U: + culture	Frontal cysts Germinolysis Altered white matter signal Ventriculomegaly Synechia in right occipital horn	NO	NO
6	Primary infection 2T (25 + 2)	Normal	Normal	26 + 5: 100	1	B: 7.72 U: + culture	Normal	NO	NO
7	Primary infection 2T (24 + 1)	Normal	Normal	28: 92.46	1	B: 3.68 U: 33,800	Normal	NO	NO
8	Primary infection 1T (9 + 1)	Normal	Punctate hypointense image in the right caudothalamic sulcus	21: 36.3	1	B: 50.2 U: 298,000	Normal	NO	NO
9	Primary infection 1T (9 + 3)	Normal	Normal	21: 71.2	1	B: 8 U: 7450	Normal	NO	NO
10	Primary infection 1T (8 + 6)	Hyperechogenicity in frontal horns Periventricular hyperechogenicity Liver calcification	Brachycephaly	21 + 3: 4130	2	B: 10.2 U: 12,000	Normal	NO	NO
11	Primary infection 2T (26 + 1)	Severe ventriculomegaly Dysgenesis and lipoma of the corpus callosum	Findings prior to maternal seroconversion: Dysgenesis and lipoma of the corpus callosum Bilateral ventriculomegaly Impaired cortical folding	29: 1.8	1	B: Negative U: 786	Findings not attributable to congenital CMV infection (dysgenesis of corpus callosum and middle line lipoma)	Mild to moderate bilateral hearing loss	Bilateral hearing loss
12	Primary infection 1T (9 + 1)	Normal	Normal	20 + 5: 30.8	1	B: 58 U: 2370	Bilateral changes in periventricular and subcortical white matter	Congenital cataracts	Congenital cataracts

(*continued*)

Table 1. Continued.

Case	Seroconversion (weeks + days of gestation)	Prenatal ultrasound	Fetal brain MRI	Amniocentesis (weeks + days of gestation: VL in $\times 10^5$ copies/ml)	Gama globulin doses (200 UI/kg)	VL in blood/urine ($\times 10^3$ copies/ml)	Neonatal brain MRI	Auditory /ophthalmological/ psychomotor development abnormalities at birth	Auditory /ophthalmological /psychomotor development abnormalities (12 months)
13	Primary infection 1T (9 + 4)	Normal	Normal	21 + 2: 62.1	1	B: 1.59 U: 28,900	Bilateral subependymal cysts Left periventricular and deep right white substance residual/ gliotic lesion	NO	NO
14	Primary infection 1T (8 + 5)	Cardiomegaly Hepatosplenomegaly Periventricular echogenicity Cysts in anterior horns	Microcephaly Altered periventricular white matter Ventriculomegaly Periventricular calcifications	34: 340	1	B: 518 U: 145,000	Extensive white matter involvement Brain atrophy Ventriculomegaly Delayed myelination	Bilateral hearing loss: severe in left ear moderate in right ear	Await tests
15	Primary infection 1T (9 + 6)	Mega cisterna magna Irregular walls of the lateral ventricles	Subcortical and subependymal cysts Posterior vermis hypoplasia	21 + 1: 30	2	B: 6.41 U: 146,000	Vacuolization Bilateral Subcortical Cysts Cerebellar vermis hypoplasia	Bilateral alteration in auditory screening	Bilateral alteration in auditory screening

B: blood; MRI: magnetic resonance imaging; T: trimester; U: urine; VL: viral load.

development except for case 14 (median age of follow-up: 7 months, IQR = 3–14).

Discussion

Treatment of pregnant women with CMV fetal infection aims at reducing symptoms at birth and the risk of long-term sequelae. Nowadays there is only experience with CMV-HIG or valaciclovir as monotherapies [4,7].

Different studies with gamma globulin or valaciclovir achieved better results when the fetuses presented no abnormalities in the ultrasound [5,7] or when those abnormalities were mild [9]. Thus, the highest risk of developing symptoms at birth appears to be among those with fetal brain echographic changes, even with prenatal monotherapy.

In this study, it was evaluated a combination treatment with CMV-HIG and valaciclovir. Despite being high-risk cases, intrauterine progression of fetal brain lesions was only observed in two cases in which the dose of CMV-HIG was repeated, slowing their progression. Although the treatment has failed to reverse ultrasound fetal lesions, only 3 out of 15 children (20%) were born with hearing impairment and their psychomotor development was consistent with chronological age in all patients but one, who also developed neurological abnormalities. This infant was born after preterm delivery with alterations in prenatal imaging tests and clinical, analytical and radiological involvement at birth occurred in a pregnant woman in whom combination therapy was initiated in the last weeks of gestation. These results contrast with a recent series using only CMV-HIG where 20% of children presented neurological abnormalities during follow-up [5]. Importantly, combination therapy was safe and did not cause relevant adverse effects in either the mothers or the fetuses.

This work has important limitations: (1) it is a non-randomized, non-controlled study, with a limited number of patients and a short-term follow-up; (2) only two-thirds of infections occurred in the first trimester of pregnancy, when there is a higher risk of long-term sequelae.

In resume, this is the first study that implements combined antiviral and immunomodulatory therapies in pregnant women with demonstrated fetal CMV-infection. Combination was well-tolerated without relevant adverse effects and could prevent the appearance of new brain lesions or the progression of existing ones. Therefore, combination therapy with valaciclovir and CMV-HIG could be a therapeutic

alternative for pregnant women with a high risk of symptomatic infection.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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