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Narrative review

Management of cytomegalovirus infection in pregnancy: is it time for valacyclovir?

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ABSTRACT

Background: Congenital cytomegalovirus (CMV) infection is the leading infectious cause of neurological impairment for which, currently, there are no approved antenatal treatment options.
Objectives: The aim of this article was to summarize the available evidence on the use of valacyclovir during pregnancy to prevent and treat congenital CMV infection and disease.
Sources: Two databases (PubMed and ClinicalTrial.gov) were reviewed.
Content: Six relevant documents were identified, namely one observational study, three clinical trials, two case reports. Most relevant findings were those from two clinical trials. A phase 2/3 placebo-controlled study showed a decrease of 71% (5 of 45 vs 14 of 47) in rate of CMV vertical transmission in women treated with 8 g/day valacyclovir following primary CMV infection in pregnancy. A phase 2, single-arm clinical trial, showed that 8 g/day valacyclovir administered to mothers of symptomatic infected foetuses increased the portion of asymptomatic neonates to 82% (34 of 41), compared with 43% (20 of 47) in untreated pregnancies from a historical cohort.
Implications: Studies in favour of using valacyclovir during pregnancy for prevention and treatment of congenital CMV infection are emerging but are still few. Randomized clinical trials on large cohorts of patients investigating the efficacy on prevention and treatment of congenital CMV are required. Unfortunately, this will be probably not be feasible at least in the short period. In the meantime, data on the 'off label' use of valacyclovir for CMV in pregnancy could be collected within a multicentre observational study. **L. Zammarchi, Clin Microbiol Infect 2020;26:1151**

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Introduction

Cytomegalovirus (CMV) is the most frequent cause of congenital viral infection [1]. Prevalence of CMV infection is around 0.5–1% of all live births, and is the leading infectious cause of sensorineural hearing loss and mental retardation [1]. Vertical transmission occurs in around 30–35% following primary infection and congenital disease in around 10–15%. In contrast, following non-primary maternal infection, foetal infection rate is estimated at around 1.2% [2].

Currently there are no approved treatment options for CMV infection during pregnancy and available guidelines recommend that any antenatal therapy should only be offered as part of a research protocol treatment [3].

Recently evidence in favour of pharmacological interventions during pregnancy is slowly growing. The aim of this article was to summarize the available evidence on the use of valacyclovir during pregnancy to prevent and treat congenital CMV infection and disease. Valacyclovir is the L-valine ester of acyclovir which shows activity against DNA polymerase of CMV, if used at high dose (i.e. 2 g every 6 h, 8 g per day). Its efficacy has been documented in several randomized studies evaluating the drug for prophylaxis of CMV reactivation in renal transplant recipients. The drug is approved in adults and adolescents above 12 years for the prophylaxis of CMV reactivation in solid organs transplanted patients at dosage of 2 g six-hourly for up to 12 weeks [4–8]. Concerning its use in pregnancy, valacyclovir is classified among group B drugs, which denotes no clear evidence of risk in humans despite the lack of controlled studies documenting safety [9,10]. Clinical data over several decades with valacyclovir and its metabolite, acyclovir, in pregnant women, have not identified a drug-associated risk of major birth defects. According to the pregnancy registry, managed by the manufacturer, the rate of birth defects among 749 women exposed to systemic acyclovir during the first trimester is not significantly different from that of the general population [10]. In a larger study conducted in Denmark, based on a nationwide registry, the rate of birth defects was not significantly different between 1561 women exposed to acyclovir in the first trimester, 2379 women exposed to acyclovir in the second and third trimesters and 835 991 unexposed pregnant women (with rates of birth defects at 2.0%, 2.0% and 2.4%, respectively) [9].

Thus, even the relatively small size of the registries had insufficient power to draw reliable or definitive conclusions regarding the safety of acyclovir or valacyclovir in pregnancy for pregnant women, the potential benefits seems to outweigh the potential risks to the foetus.

In this article we reviewed the available evidence on the efficacy of valacyclovir in pregnancy for CMV infection.

Methods

A PubMed search was conducted using the following search strategy ((valacyclovir) AND (pregnancy OR pregnant OR congenital) AND (cytomegalovirus OR CMV)). Moreover, we screened the ClinicalTrial.gov database using the word 'cytomegalovirus' to identify additional relevant documents.

Results

One observational study, two clinical trials and two case reports were identified in PubMed [11–15]. Moreover, one trial reporting the effect of valacyclovir for the prevention of vertical transmission of CMV was identified in ClinicalTrial.gov and their preliminary findings, published in *Open Forum Infectious Diseases* in October 2019, were retrieved [16].

Summary of the identified studies

Observational study

In 2007, a group of French researchers first reported observational data on the use of high-dose valacyclovir in 20 pregnant women with 21 foetuses with symptomatic congenital CMV infection. The treatment was administered on the basis of compassionate care when parents chose to continue with their pregnancies [11]. Inclusion criteria for treatment were confirmed congenital CMV infection (CMV-DNA positive from amniotic fluid) with biomarkers and/or ultrasound markers of foetal infection following primary maternal CMV infection (Table 1). Standard management of infected foetuses included foetal blood sampling at diagnosis, and 4–6 weeks later, to determine the platelet count and gamma-glutamyl transpeptidase (GGT) plasma concentration at baseline and their changes over time. Foetal thrombocytopenia below 100,000/dL and/or elevated GGT were considered to be biomarkers of a symptomatic foetal infection.

Treatment was started at a median of 28 weeks of pregnancy (range 22–34) and continued for a median of 7 weeks (range 1–12 weeks). Therapeutic concentrations of valacyclovir were achieved in maternal and foetal bloods, and viral load in foetal blood decreased significantly after treatment. No difference in the rate of poor outcome was observed by comparing with a historical cohort of 24 singleton pregnancies that presented with symptomatic intrauterine CMV infection before valacyclovir treatment was offered or declined. No maternal, foetal, or neonatal adverse effects were reported.

Clinical trials

In the following years, the same research group designed a randomized controlled trial (Cymeval NCT01037712) comparing

Table 1
Foetal signs used as inclusion criteria for treatment with valacyclovir during pregnancy in case of confirmed foetal cytomegalovirus infection

Jacquemard *et al.* 2007 [11]	
Foetal ultrasound markers	Grade 3 hyperechogenic bowels
	Ascites
	Growth restriction with an estimated foetal weight below the 10th percentile
	Ventriculomegaly with ventricular width of at least 10 mm at the level of the atrium
	Any other brain anomaly
And/or laboratory findings of CMV infection in foetal blood	Foetal elevated GGT
	Foetal platelet count <100,000/μL
Leruez-Ville et al. 2016 [12]	
At least one extracerebral abnormality compatible with foetal CMV infection	Foetal growth restriction
	Abnormal amniotic fluid volume
	Ascites and/or pleural effusion
	Skin edema
	Hydrops
	Placentomegaly (thickness >40 mm)
	Hyperechogenic bowel
	Hepatomegaly (maximum diameter >40 mm)
	Splenomegaly (maximum diameter >30 mm)
	Liver calcifications
And/or one isolated cerebral abnormality	Moderate isolated ventriculomegaly (<15 mm)
	Isolated cerebral calcification
	Isolated intraventricular adhesion
	Vasculopathy of lenticulostriate vessels
And/or laboratory findings of generalized CMV infection in foetal blood	Foetal viremia >3000 copies/mL
	Foetal platelet count <100,000/μl

CMV, cytomegalovirus; GGT, gamma-glutamyl transpeptidase.

prenatal treatment with valacyclovir against placebo in moderately symptomatic infected foetuses, that failed to recruit because women declined randomization. The authors opted for a different study design, a phase II open label trial with only one arm based on a Simon optimal two-stage design (Cymeval II NCT01651585) using a historical cohort as comparator [12]. In the study, high dose valacyclovir (8 g per day) was used in 40 women with primary CMV infection to treat 41 foetuses presenting with symptomatic congenital CMV infection. Inclusion criteria for treatment were confirmed congenital CMV infection (CMV-DNA positive amniocentesis) and presence of foetal signs of infection (Table 1). Only moderately symptomatic foetuses were included, while asymptomatic foetuses (those without any ultrasound or foetal blood alteration), as well as those with severe cerebral ultrasound abnormalities, were excluded. Treatment was started at a median of 22 weeks of pregnancy (range 22–35 weeks) and continued for a median of 89 days (range 41–102 days). A significant decrease in foetal blood viral load and a significant increase in platelet count were observed between the time of treatment initiation and birth. The proportion of asymptomatic neonates was 82% (34 of 41). These data were compared with a historical cohort obtained by a systematic review of the literature which included three published case series [11,17,18], reporting 724 pregnancies with a maternal CMV primary infection, 217 with an infected foetus of which 47 with ultrasound abnormalities matching the inclusion criteria required (moderately symptomatic foetuses).

Among them 20 (43%) neonates were born asymptomatic. In conclusion, the valacyclovir treatment significantly increased the portion of asymptomatic neonates from 43%, without treatment, to 82% with treatment. There was no overlap in 95% confidence intervals. Treatment adherence was >90%, two women reported headache, a not clinically relevant increase in median maternal alanine and aspartate aminotransferase level (values < 40 UI/L) was observed after 3 months of treatment. No creatinine level increase was reported.

In a randomized controlled trial (NCT00530777) carried out in Nairobi, Kenya, published in 2014, valacyclovir, at a dosage of 500 mg twice daily, was used in 74 HIV-1 and HSV-2 co-infected pregnant women starting from 34 weeks of gestation and continued for 12 months postpartum [13]. The trial was primarily designed in order to evaluate whether HSV-2 suppression reduces maternal HIV-1 RNA levels during pregnancy and breastfeeding, but effect on CMV was also evaluated. Maternal valacyclovir had no effect on timing of infant CMV acquisition or breast milk CMV viral loads, although it modestly reduced cervical CMV shedding. Valacyclovir was not associated with infant or maternal toxicities or adverse events, and no congenital malformation was observed.

Recently, the results of a randomized, double-blind, phase 2/3 placebo-controlled study (NCT02351102) investigating the effect of valacyclovir to prevent vertical transmission of cytomegalovirus, was preliminarily published in *Open Forum Infectious Diseases* [16]. In the study, 90 pregnant women (92 foetuses, two twin pregnancies) were randomized 1:1 to receive high-dose valacyclovir (8 g per day) or placebo following primary CMV infection during the periconceptional period or the first trimester. Treatment was initiated at the time of serological diagnosis of primary infection and continued until amniocentesis. Amongst the valacyclovir group, five of 45 (11.1%) amniocenteses were positive for CMV, compared with 14 of 47 (29.8%) in the placebo group (P GLMM = 0.03), corresponding to an odds ratio of 0.29 (95% confidence interval: 0.09–0.90) for vertical CMV transmission (reduction rate of 71% in foetal transmission). Further data on follow-up are currently not available.

Case reports

High-dose valacyclovir was used in a woman who was accidentally discovered to be pregnant (13 weeks) 5 days after receiving a kidney live-related renal transplant from her father for chronic kidney disease [15]. The recipient was CMV seronegative and the donor was CMV seropositive. The woman received valacyclovir prophylaxis at dosage of 8 g per day for 12 weeks and cyclosporine. She remained CMV seronegative throughout pregnancy, the baby was born healthy and no apparent adverse effect on mother or foetus was observed.

Another immunocompetent pregnant woman, who acquired primary CMV infection at 17 weeks + 5 days of pregnancy, was treated with high-dose valacyclovir (8 g per day), starting from the 19 weeks + 6 days of pregnancy [14]. Treatment was continued until 24 weeks of pregnancy + 2 days, when a negative result of PCR for CMV on amniotic fluid was obtained. The patient did not develop any side effects and delivered at 41 weeks + 2 days an uninfected baby. CMV polymerase chain reaction assays, in urine and saliva, were both negative at birth.

Discussion

Currently, there is still no treatment approved for CMV in pregnancy. The growing evidence for the benefit of the use of high-dose valacyclovir in this setting raises the question about the ethnicity of not considering this off-label treatment for pregnant women with primary infection acquired in the first trimester to prevent vertical transmission, or for pregnant women with confirmed mild to moderate symptomatic foetal infection, who want to continue the pregnancy.

It should be remembered that interesting, though conflicting, data on CMV-specific hyperimmune globulin (HIG) for pregnant women with primary CMV infection are also available. Some observational studies have shown that CMV-specific HIGs are associated with a significant reduction in maternal-to-foetal transmission and severity of congenital infection [19–22]. A randomized trial did not demonstrate a significant benefit on CMV mother-to-child transmission of CMV-specific HIGs at a dose of 100 IU/kg every 4 weeks following primary maternal infection. In this study, overall rate of congenital infection was indeed similar for both the placebo and the treatment groups [23]. The proportion of infected infants symptomatic at birth was also similar for both groups. There were also no differences in the viral or immune characteristics of infected infants between the two groups and in the viral load and histological damage between placentas from women who transmitted the infection and those who did not transmit neither among HIG-treated nor untreated mothers [24]. In addition, the number of obstetric adverse events was higher in the HIG group than in the placebo group (13% vs 2%) [23]. A recent multicentre Spanish study confirmed that treatment of primary maternal infection with CMV-specific HIG did not affect the rate of congenital infection [25]. However, data from a very recent non-randomized study showed that biweekly administration of CMV-specific HIG at a dose of 200 IU/kg following primary maternal infection prevents maternal–foetal transmission up to 20 weeks of gestation [19]. These contrasting data need to be further investigated in a randomized clinical trial on a large cohort.

From a practical point of view, valacyclovir treatment may present some advantages compared with CMV-specific HIG, namely the oral route of administration and the markedly lower cost. In our setting, considering that a 1-g tablet of valacyclovir costs about 0.28 Euro (price list of the hospital pharmacy of the Careggi University Hospital, Florence, Italy), a 12-week treatment

course would cost about 188 Euros. Conversely, as one 1000-UI vial of CMV-specific HIG costs about 216 Euros, a treatment course of three 200-UI/kg infusions (that used by Kagan et al. [19]) or a course of five 100-UI/kg infusions (that used by Revello et al. [23]) would cost 7128 and 5940 Euros, respectively, considering a woman of 55 kg of body weight. These considerations have to be taken into account when approaching the problem of CMV infection in pregnancy from a public health perspective.

Thus far, universal serological screening for CMV in pregnancy is not recommended, but the recent findings by Shahar-Nissan and colleagues might completely change the attitude towards this approach. Cost and the cost-effectiveness of testing and treatment for CMV during pregnancy should be assessed, once more solid evidence on treatment interventions will be available. An economic analysis, conducted in the US, reported that universal maternal serology screening would be cost-effective if a prevention strategy could lead to a reduction in mother to foetus transmission of more than 47% [26]. Moreover, the possible role of CMV-specific HIG seems to be mainly confined to the prevention of vertical transmission during a primary infection because humoral immunity has a limited role in the control of latent CMV infection and viraemia which are mainly influenced by cellular immunity [27]. Conversely, valacyclovir could be more effective in reducing viraemia being probably useful both in prevention and in treatment of CMV congenital infection [27].

In conclusion, studies in favour of using valacyclovir during pregnancy for prevention and treatment of congenital CMV infection in women who want to continue the pregnancy are emerging but are still few. Randomized clinical trials on large cohorts of patients investigating the efficacy on prevention and treatment of congenital CMV are required. Unfortunately, a similar trial will probably not be easy to organize, at least in the short period.

In the meantime, the recent case report published by Codaccioni and collegues [14] showed that some clinicians started using 'off-label' valacyclovir treatment during pregnancy for CMV infection.

Data on this 'off-label' treatment could be collected within a multicentre observational study because these data could corroborate currently available evidence from the few clinical trials available.

Transparency declaration

The authors declare that they have no conflicts of interest related to the article content.

Authors' contributions

L.Z. conceived of the review, performed the systematic analysis of literature and data extraction and drafted the manuscript. M.S.T and A.B wrote the manuscript. M.A., I.C., L.P., M.D.T., G.S., L.T., F.C., L.G., B.B., P.C. and M.T. critically reviewed the discussed the manuscript.

References

[1] Benoist G, Leruez-Ville M, Magny JF, Jacquemard F, Salomon LJ, Ville Y. Management of pregnancies with confirmed cytomegalovirus fetal infection. Fetal Diagn Ther 2013;33:203–14.
[2] Emery VC, Lazzarotto T. Cytomegalovirus in pregnancy and the neonate. F1000Res 2017;6:138.
[3] Hughes BL, Gyamfi-Bannerman C. Diagnosis and antenatal management of congenital cytomegalovirus infection. Am J Obstet Gynecol 2016;214:B5–11.
[4] Kalil AC, Levitsky J, Lyden E, Stoner J, Freifeld AG. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. Ann Intern Med 2005;143:870–80.
[5] Lowance D, Neumayer HH, Legendre CM, Squifflet JP, Kovarik J, Brennan PJ, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International valacyclovir cytomegalovirus prophylaxis transplantation study group. N Engl J Med 1999;340:1462–70.
[6] Reischig T, Hribova P, Jindra P, Hes O, Bouda M, Treska V, et al. Long-term outcomes of pre-emptive valganciclovir compared with valacyclovir prophylaxis for prevention of cytomegalovirus in renal transplantation. J Am Soc Nephrol 2012;23:1588–97.
[7] Reischig T, Jindra P, Hes O, Svecova M, Klaboch J, Treska V. Valacyclovir prophylaxis versus preemptive valganciclovir therapy to prevent cytomegalovirus disease after renal transplantation. Am J Transplant 2008;8:69–77.
[8] Reischig T, Kacer M, Jindra P, Hes O, Lysak D, Bouda M. Randomized trial of valganciclovir versus valacyclovir prophylaxis for prevention of cytomegalovirus in renal transplantation. Clin J Am Soc Nephrol 2015;10:294–304.
[9] Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. JAMA 2010;304:859–66.
[10] Glaxo Wellcome Inc. Valtrex (valacyclovir hydrochloride). Prescribing information; 2013.
[11] Jacquemard F, Yamamoto M, Costa JM, Romand S, Jaqz-Aigrain E, Dejean A, et al. Maternal administration of valaciclovir in symptomatic intrauterine cytomegalovirus infection. BJOG 2007:1113–21.
[12] Leruez-Ville M, Ghout I, Bussieres L, Stirnemann J, Magny JF, Couderc S, et al. In Utero treatment of congenital cytomegalovirus infection with valacyclovir in a multicenter, open-label, phase II study. Am J Obstet Gynecol 2016;215:462 e1–462 e10.
[13] Roxby AC, Atkinson C, Asbjornsdottir K, Farquhar C, Kiarie JN, Drake AL, et al. Maternal valacyclovir and infant cytomegalovirus acquisition: a randomized controlled trial among HIV-infected women. PloS One 2014;9:e87855.
[14] Codaccioni C, Vauloup-Fellous C, Letamendia E, Saada J, Benachi A, Vivanti AJ. Case report on early treatment with valaciclovir after maternal primary cytomegalovirus infection. J Gynecol Obstet Hum Reprod 2019;48:287–9.
[15] Hold PM, Wong CF, Dhanda RK, Walkinshaw SA, Bakran A. Successful renal transplantation during pregnancy. Am J Transplant 2005;5:2315–7.
[16] Shahar-Nissan K, Pardo J, Peled O, Krause I, Bilavsky E, Bilavsky E, et al. Valacyclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy. Open Forum Infect Dis 2019;6:S1002.
[17] Guerra B, Simonazzi G, Puccetti C, Lanari M, Farina A, Lazzarotto T, et al. Ultrasound prediction of symptomatic congenital cytomegalovirus infection. Am J Obstet Gynecol 2008;198:380 e1–7.
[18] Picone O, Simon I, Benachi A, Brunelle F, Sonigo P. Comparison between ultrasound and magnetic resonance imaging in assessment of fetal cytomegalovirus infection. Prenat Diagn 2008;28:753–8.
[19] Kagan KO, Enders M, Schampera MS, Baeumel E, Hoopmann M, Geipel A, et al. Prevention of maternal-fetal transmission of cytomegalovirus after primary maternal infection in the first trimester by biweekly hyperimmunoglobulin administration. Ultrasound Obstet Gynecol 2019;53:383–9.
[20] Nigro G, Adler SP, La Torre R, Best AM. Passive immunization during pregnancy for congenital cytomegalovirus infection. N Engl J Med 2005;353:1350–62.
[21] Nigro G, Adler SP, Parruti G, Anceschi MM, Coclite E, Pezone I, et al. Immunoglobulin therapy of fetal cytomegalovirus infection occurring in the first half of pregnancy—a case-control study of the outcome in children. J Infect Dis 2012;205:215–27.
[22] Visentin S, Manara R, Milanese L, Da Roit A, Forner G, Salviato E, et al. Early primary cytomegalovirus infection in pregnancy: maternal hyperimmunoglobulin therapy improves outcomes among infants at 1 year of age. Clin Infect Dis 2012;55:497–503.
[23] Revello MG, Lazzarotto T, Guerra B, Spinillo A, Ferrazzi E, Kustermann A, et al. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. N Engl J Med 2014;370:1316–26.
[24] Gabrielli L, Bonasoni MP, Foschini MP, Silini EM, Spinillo A, Revello MG, et al. Histological analysis of term placentas from hyperimmune globulin-treated and untreated mothers with primary cytomegalovirus infection. Fetal Diagn Ther 2019;45:111–7.
[25] Blazquez-Gamero D, Galindo Izquierdo A, Del Rosal T, Baquero-Artigao F, Izquierdo Mendez N, Soriano-Ramos M, et al. Prevention and treatment of fetal cytomegalovirus infection with cytomegalovirus hyperimmune globulin: a multicenter study in Madrid. J Matern Fetal Neonatal Med 2019;32:617–25.
[26] Cahill AG, Odibo AO, Stamilio DM, Macones GA. Screening and treating for primary cytomegalovirus infection in pregnancy: where do we stand? A decision-analytic and economic analysis. Am J Obstet Gynecol 2009;201:466 e1–7.
[27] Baraniak I, Kropff B, Ambrose L, McIntosh M, McLean GR, Pichon S, et al. Protection from cytomegalovirus viremia following glycoprotein B vaccination is not dependent on neutralizing antibodies. Proc Natl Acad Sci U S A 2018;115:6273–8.