

Antiviral medication to prevent fetal transmission of maternal CMV during pregnancy

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ABSTRACT

Background. Cytomegalovirus infection represents the most frequent congenital viral infection, with serious consequences on newborns. Neurosensorial hearing loss is the principal outcome, but also, the infection can cause other central nervous system's anomalies. Although CMV infection can have a major impact on fetal development, there are not clear directions to follow yet, to prevent or treat this condition. Therefore, our purpose with this paper is to update the knowledge regarding the treatment options in order to prevent fetal transmission of maternal CMV infection, based on the latest data from the specialized literature in this field.

Methods. Electronic research and analysis of the relevant articles published mainly in the last 5 years were performed, consulting the web platforms PubMed, ScienceDirect, Mendeley and ClinicalTrials.gov.

Results and conclusions. To date, there is not enough evidence to reach a consensus on therapeutic methods to prevent or to treat fetal CMV infections and, as a consequence, antenatal screening is not justified. Many pharmaceutical companies work on vaccines to prevent CMV infection, but the results are only from studies' second phase. Information on efficiency of hyperimmunoglobulin is mixt and it is necessary to clarify the dosage. Among antiviral agents, valaciclovir, which was studied in recent clinical trials, seems to have the best efficiency to prevent fetal transmission of maternal CMV infection and the best safety profile. Valganciclovir has possible embryotoxic effects, but higher potency and information on it are available only from case reports. The interest of scientific community on this topic is high, thus many studies are underway to bring new clarifications.

Keywords: cytomegalovirus/CMV, pregnancy, maternal fetal transmission, prevention

INTRODUCTION

Cytomegalovirus (CMV) or Herpesvirus 5 infection has a global prevalence between 50% and 85% [1] and it is the most frequent viral congenital infection. It is estimated that 1 in 150 children is born with congenital CMV infection. This is the main cause of neurosensorial non-genetic hearing loss and it can also cause anomalies of cognitive development or cerebral palsy [2,3]. Maternal CMV infection is usually asymptomatic (about 80%) and because of that, it is diagnosed only when fetal signs are noticed [4]. Although this subject has an impor-

tant impact, to date, there is no efficient approved treatment to prevent this infection on pregnant women [5]. This is the reason why there is no screening program. Our paper intends to reveal the latest conclusions on the antiviral medication's efficiency in order to prevent fetal transmission of maternal CMV infection.

METHODS

We consult the specialized literature on this topic, performing electronic research on web platforms

PubMed, ScienceDirect, Mendeley and ClinicalTrials.gov. The key words that we use were cytomegalovirus/CMV, pregnancy, materno-fetal transmission, prevention. The results of our research were filtered and we chose only the relevant articles published mainly in the last 5 years. Following analysis of selected articles, we identified the most valuable results and scientific opinions, we compared and discussed them, and the information that we obtained is presented below.

PRIMARY PREVENTION

Even if CMV infection is the most frequent neonatal infection and has severe consequences, child-bearing age women are not informed enough about the ways of the disease transmission and astonishingly, their knowhow about CMV infection is lower in the last years (from 14% in 2005 to 9% in 2016). The main responsibility is on their attending physicians, who do not offer them an adequate counseling [6]. The knowhow and application of hygiene rules while women take care of young children can decrease the seroconversion rate from 7,6% (in uncounseled groups) to 1,2% (in counselled groups) [4]. The measures that can limit the transmission of CMV infection are: frequent handwash with water and soap after changing diapers, feeding young children, contact with pacifiers, toys, clothes, surfaces than can be contaminated with saliva, urine or nasal secretions; frequent cleaning of possible contaminated objects, avoiding sharing cutlery, toothbrush or other intimate objects [2]. Another method of primary prevention is vaccination, but to date, this is not available. Research is ongoing, but phase III results are not available yet. Six vaccines are involved in advanced clinical trials (Sanofi Pasteur, MSD, City of Hope Triplex Vaccine, City of Hope Cytomegalovirus PepVax, Hookipa Pharma, Astellas), another 3 products are involved in incipient clinical studies and other 2 preparations are in preclinical researches. Their early phase II conclusions show that vaccination can prevent CMV infection in seronegative patients who have been exposed to the virus and in seronegative patients who suffered organ or bone marrow transplant [7].

SECONDARY PREVENTION

At this moment, the options to prevent maternal-fetal transmission are limited and they are still under study. The two alternatives are Hyperimmunoglobulin (HIG) or antiviral agents.

HIG is an immunoglobulin G derived preparation, from high concentration of anti-CMV antibody human plasma. This might decrease fetal CMV transmission through neutralization of the virus by

the high avidity antibodies [2]. First research found a half time of 22 days and, consequently, HIG was administered once at 4 weeks, 100U/kg, intravenous. Nigro et al. reported a decrease in transmission rate from 40% in control group to 16% in study group [8]. For the same posology, Revello et al. found a decrease of only 30%, versus 44% in placebo group, but they noticed an increase of obstetrical complications such as preterm birth, preeclampsia, or intrauterine growth restriction [1,9,10]. Recently, it has been discovered that half time of HIG is about 11 days and consequently, it is necessary to administer one dose once at 2 weeks. Kagan et al. increased the dose to 200 U/kg, once at 2 weeks, starting before 14 weeks of gestation and until 20 weeks, and so they reported a transmission rate of 7,5% comparing with 35,2% in control group and they did not notice a higher proportion of obstetrical complications [1,11].

The alternative treatment option, cheaper and more studied is represented by antiviral drugs. Antiviral agents, administered to provide secondary prevention, try to treat maternal infection by lowering the viremia and thus, they decrease the risk of viral transmission to the fetus, through the placenta. Only one drug was studied in clinical trials with pregnant women to date and this is valacyclovir. The other medicines available to treat CMV infection are ganciclovir, valganciclovir, foscarnet, cidofovir, maribavir, letermovir and fomivirsen, but they do not prove their safety and/or efficiency to be used in pregnancy and the studies are ongoing [2,12].

Ganciclovir and its pro-drug, valganciclovir are the most efficient antiviral agents available to treat CMV infection and they act through inhibition of viral DNA polymerase. Because of the low intestinal absorption of ganciclovir (8% bioavailability), its L-valine ester, valganciclovir, is preferred to use for oral administration [5]. These two substances seem to have teratogenic and cytotoxic effects and they are classified by Therapeutic Goods Administration Australia in class D [1,13].

Valaciclovir is L-valine ester of acyclovir, is metabolized by liver, but with a higher oral bioavailability (50% versus 10-20%) and its mechanism of action is also inhibition of viral DNA polymerase. It is renally excreted, through glomerular filtration and tubular secretion. This substance is approved to use in adults and adolescents over 12 years, but the efficiency is under ganciclovir. In vitro and animal studies prove a good safety profile, without genotoxic or carcinogenic effects. For use in pregnancy, ganciclovir is classified in class B of safety [1,3,14,15]. Fourteen years ago The Acyclovir in Pregnancy Registry was established and 1234 pregnant women who received acyclovir in any of the three trimesters

ters of pregnancy, from 24 countries, were followed. The researchers noticed that the rate and types of major defects of these fetuses, who were exposed in utero to acyclovir, were not different from the general population [16].

An inconvenient can be the large number of tablets which must be swallowed daily, the dose is 8g/day, which means 16 tablets. However, the adherence to treatment of pregnant women was increased [3].

The experience and the evidence of valaciclovir use to prevent fetal transmission of CMV maternal infection are supported by a couple of cases and some recent clinical trials. In 2020, an Italian group reported the first series of cases treated with valaciclovir for secondary prevention of congenital CMV infection. It identify 12 pregnant women with primary CMV infection in first trimester of pregnancy, who received 8 g valaciclovir/day starting right after the moment of diagnosis and until amniocentesis. For two cases with positive PCR tests in amniotic fluid, treatment was continued until delivery. After birth, 3 more infected fetuses were identified, but asymptomatic, after a negative result of amniocentesis. Only one new-born of the two confirmed by amniocentesis have developed unilateral moderate hearing loss at 18 months old. Data obtained in this way was compared with an older batch of the same clinic and the following results were configured: the transmission rate at the time of amniocentesis was 17%, half compared to 37% of the control batch, and after birth 42%, but also considering a false negative amniocentesis rate of 30%. Of the 3 patients with viremia re-detectable after stopping treatment, 2 of them gave birth to infected fetuses, thus demonstrating a delayed transmission of the virus to the fetus. This data is not statistically significant due to the small number of cases. The authors do not report any adverse effects attributable to valaciclovir [17].

In September 2020, the results of the first randomized, double-blind, placebo-controlled trial conducted in Israel between 2015-2018 (NCT02351102) on 90 patients with CMV infection detected periconceptionally or in the first trimester of pregnancy were reported [18]. Treatment with 4g valaciclovir x 2 / day was initiated in 45 cases from the first post-diagnosis visit and lasted until the time of amniocentesis, accumulating at least 7 weeks and reaching 21 weeks gestational age. In the study group, a total of 5 positive results for CMV at amniocentesis were detected, out of 45 achieved (11%), compared to the control group, with 14 out of 45 (30%), $p = 0.027$. No significant differences were noticed for periconceptional infections, the positive results were 3 out of 26 amniocentesis (12%) versus 3 out of 24 (13%), $p = 0.91$, but for infections acquired in the

first trimester a reduction in CMV transmission of at 48% (11 out of 23 positive results in the control group) at 11% (2 out of 19 in the valaciclovir group), $p = 0.020$. It was concluded that patients with periconceptional infection started treatment later than the time of contacting CMV (on average at 60.58 days) and thus the positive results in amniocentesis are more numerous, while pregnant women diagnosed in the first trimester of pregnancy began treatment closer to the time of infection (on average 43.84 days) and thus the efficiency was higher and the percentage of positive results much lower. Post-partum, 7% of symptomatic fetal infections were reported in the study group, compared with 16% in the placebo group. Out of a total of 6 positive CMV cases despite negative amniocentesis, 4 cases were reported in the valaciclovir group and 2 in the control group. The noticed side effects (thrombocytopenia, headache, nausea, abdominal pain) were not clinically significant. Shadar-Nissan et al. demonstrated the effectiveness of using valaciclovir in preventing the fetal transmission of maternal CMV infection and draw attention to the timing of treatment. The conclusion is that the effectiveness of the treatment will be higher if it is initiated as early as possible before the time of diagnosis [18].

A few months ago, Faure-Bardon et al. confirmed the benefit of valaciclovir for the secondary prevention of congenital CMV infection through a case-control study conducted between 2009-2020 [15]. During this period, 310 primary maternal infections were detected and 65 of these patients received valaciclovir 8 g/day. The results were compared with 65 control cases. The duration of treatment was, on average, 35 days, and the average time of onset was 12.71 weeks gestational age. The transmission rate was 12% (8/65) in the study group, compared to 29% (19/65) in the control group, thus concluding there was a significant decrease in the vertical transmission of maternal-fetal CMV infection (OR = 0.318 [0.12-0.841], $p = 0.021$). This group of authors also notes a greater effect of treatment in reducing the transmission of contact infection in the first trimester of pregnancy versus periconceptional, but they attribute it to the lower background risk of transmitting periconceptional infections. Regarding the safety of administration, there was a case of acute oliguric renal failure after 4 weeks of valaciclovir administration, but it was remitted 10 days after stopping treatment. The possible mechanism was considered the accumulation and precipitation of crystals in the proximal tubular renal cells. One opinion is that the dose of 8 g/day should be divided into 4 doses of 2 g each, the half-life of valaciclovir being 3 hours and thus decreasing the risk of accumulation and local renal toxicity. Therefore, careful monitoring of creatinine is recommended during treatment with valaciclovir [15].

Although still in incipient state, studies on placental cell cultures testing CMV-specific antivirals are ongoing. An analysis of the effects of letermovir, maribavir, cidofovir, acyclovir, and ganciclovir on first-trimester TEV-1 trophoblastic cell cultures and third-trimester ex vivo placental explant histocultures was performed. They were found to have no cytotoxic effects and did not affect cell proliferation. Antiviral treatment of CMV-infected placental explants resulted in a statistically significant inhibition ($p < 0.05$) of viral replication in 83.3% for letermovir, 83.6% for maribavir, 89.3% for cidofovir, 82.4% for ganciclovir, but not for acyclovir [12].

POSTNATAL TREATMENT OF CMV INFECTION

Hyperimmunoglobulin and antivirals (ganciclovir/valganciclovir) remain the only tools to be used for confirmed fetal CMV infection.

HIG was most often evaluated in studies that investigated mainly the effect of decreasing the maternal-fetal transmission rate, but which also analyzed the effect in case of confirmed fetal infection. Therefore, there is research which identifies a lower percentage of infected fetuses, but asymptomatic, among pregnant women who received treatment with HIG, compared to those whose mothers were not treated with HIG, but there are also results that show no significant difference [2].

Regarding antiviral therapy initiated antepartum, there is mixed information. An observational pilot study did not show significant differences in new-born symptoms whose mothers received valaciclovir during pregnancy (47.6%) compared to untreated cases (41.7%) [2], while Leruez-Ville's group provided results deriving from a phase II multicenter study, which show a positive association between the antenatal administration of 8 g/day valaciclovir and the birth of an asymptomatic new-born (82%), compared with 43% - the percentage of a control cohort without treatment [19].

Ganciclovir and valganciclovir are the preferred drugs for neonatal treatment of CMV infection. In-

ternational recommendations and guidelines are in favor of administration of a dose of 16 mg valganciclovir/kg x2/day, orally, between 6 weeks and 6 months to symptomatic newborns, starting from first month of life. If the condition does not allow it, ganciclovir iv, 6mg/kg x2/ day can be administered in the first 2 weeks of treatment and then a switch to oral medication is recommended [6,20]. The aim is to prevent the onset of deafness or to prevent it from getting worse, in cases where it is already present. Although this is the recommended therapy, cases of resistance to treatment (approximately 4%) are also reported [6,21]. Studies to determine the effectiveness of valganciclovir in infected but asymptomatic or isolated deaf newborns are ongoing (NCT03301415, NCT03107871, NCT01649869) [22,23,24], and a study evaluating the pharmacokinetics of letermovir in the treatment program is scheduled for 2022 [1,6].

CONCLUSIONS

Currently, advice and education of patients on applicable hygiene measures remain the most accessible and safe methods of preventing CMV infection during pregnancy. At present, there are insufficient reliable data to recommend treatment with hyperimmunoglobulin or a specific antiviral agent for the prevention of maternal-fetal transmission or the treatment of confirmed fetal infection. However, the results reported so far are favorable and promising. Numerous studies are underway and we expect soon changes in the recommendation of screening, the possibility of vaccination, but also treatment to limit as much as possible the serious effects of this congenital infection.

Rog adaptarea bibliografiei criteriilor PubMed, potrivit exemplului de mai jos:

Leruez-Ville M, Foulon I, Pass R, Ville Y. Cytomegalovirus infection during pregnancy: state of the science. *Am J Obstet Gynecol.* 2020 Sep;223(3):330-349. doi: 10.1016/j.ajog.2020.02.018. Epub 2020 Feb 24. PMID: 32105678.

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