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Updates of Congenital Cytomegalovirus (cCMV) infection

Literature Review

Maged Naser[1], Mohamed M. Nasr[2], Lamia H. Shehata[3]

[1] Mazahmiya Hospital, Ministry of Health, Kingdom of Saudi Arabia, Department of Ob/Gyn,

[2] King Fahd Hospital, Ministry of Health, Kingdom of Saudi Arabia, Department of Surgery, Consultant Endoscopic Surgery,

[3] Department of Radiology, Care National Hospital, KSA of Radiology.

Abstract – Congenital cytomegalovirus (cCMV) infection is the most well-known congenital viral disease and is the main non-genetic reason for sensorineural hearing loss (SNLH) and a significant reason for neurodevelopmental inabilities. The gamble of intrauterine transmission is most elevated when vertical infection happens during pregnancy, with a higher pace of vertical transmission in mothers with more established gestational age at infection, while the gamble of unfriendly fetal impacts fundamentally increments on the adverse effects that fetal infection happens during the first half of pregnancy. Although, its prevalence and morbidity among the neonatal populace, there isn't yet a standardised diagnostic test and therapeutic methodology for cCMV infection. This review expects to investigate the most recent improvements in the diagnosis and treatment of cCMV infection. literature shows that preventive interventions other than behavioural measures during pregnancy are as yet lacking, albeit numerous clinical preliminaries are right now progressing to plan vaccination for women before pregnancy. As of now, we suggest utilizing a PCR measure in blood, urine, and saliva in neonates with suspected cCMV infection. As of now, there is no proof of the advantage of antiviral treatment in asymptomatic infants. On account of symptomatic cCMV, we really suggest treatment with oral valganciclovir for a length of a year. The adequacy and tolerability of this treatment choice have demonstrated successful for hearing and neurodevelopmental long-term results. Valganciclovir is saved for congenitally infected neonates with the symptomatic infection at birth, like microcephaly, intracranial calcifications, unusual cerebrospinal fluid index, chorioretinitis, or sensorineural hearing loss. Treatment with antiviral medications isn't regularly recommended for neonates with the mildly symptomatic infection at birth, for neonates under 32 weeks of gestational age, or for infants over 30 days old due to deficient proof from studies. In any case, since these populaces represent by far most of neonates and infants with cCMV disease and they are in risk of developing late-onset sequelae, a biomarker ready to foresee long-term sequelae ought to likewise be found to justify beginning treatment and decreasing the burden of CMV-related complications.

Keywords – Antiviral Treatment; Cytomegalovirus; Congenital CMV.

I. INTRODUCTION

Neonatal infection; vertical transmission countries by adulthood and almost everybody by an early childhood in low-and middle-income countries [1,2]. CMV infection passes undetected in healthy children and adults. In any case, a few high-risk gatherings, including immunocompromised organ transplant recipients, hematopoietic stem cell transplant recipients, and individuals infected with human immunodeficiency infection (HIV), are at risk of developing life-threatening and sight threatening CMV disease [3]. CMV is likewise a significant reason for morbidity and occasional mortality in neonates. Lately, it has become obvious that congenital CMV (cCMV) infection is the most well-known congenital viral disease, with an expected birth prevalence of 0.2-6% in industrialized countries [4], while restricted studies in non-industrial countries (Asia, Africa, Latin America) have shown a prevalence going from 0.6% to 6.1% [5]. cCMV adds to a high burden of disease and is the main non-

Corresponding Author: Maged Naser

genetic reason for sensorineural hearing loss (SNLH) and a significant reason for neurodevelopmental disabilities in children [6-8].

Intrauterine CMV transmission might happen in mothers without prior immunity who first gained CMV infection in pregnancy (primary infection) or in women with prior antibodies to CMV either by reactivation of a past maternal disease or by the acquisition of an alternate viral strain (non-primary infection) [9]. The gamble of intrauterine transmission is most elevated when primary infection happens during pregnancy, with a higher pace of vertical transmission in mothers with older gestational age at infection, while the gamble of unfavorable fetal impacts fundamentally increments if fetal infection happens during the first half of pregnancy [10-13].

A significant determinant of cCMV is the prevalence of maternal CMV infection in the populace. Among low seroprevalence populaces, one-half to three-quarters of all congenital infections among newborns are because of non-primary infection during pregnancy, while in populaces with high maternal sero-immunity, practically all congenital infections happen because of non-primary infection. Therefore, countries with high seroprevalence have high paces of congenital infection, even though the gamble of infecting the fetus is higher in cases of primary infection [14]. In addition, some headway has been made in treating symptomatic newborns with cCMV. This review means to explore the most recent improvements in the diagnosis and treatment of congenital CMV infection.

II. Clinical Picture

Congenital infection might be named symptomatic or asymptomatic, even though there is no reasonable meaning of these two groupings in the literature. As a rule, moderately to seriously indicative cCMV is characterized as babies who have numerous signs or central nervous system (CNS) involvement; mildly symptomatic cCMV is characterized as infants who have one or two of confined manifestations that are mild and transient; asymptomatic cCMV with isolated sensorineural hearing loss (SNHL) is characterized as infants who have no evident clinical symptoms other than hearing loss; asymptomatic cCMV is characterized as infants who have no clear abnormalities at birth and have normal hearing [15]. Among congenitally infected infants, around 10-15% have symptoms and signs of the disease at birth, and roughly half experience long term sequelae [16,17]. It is anticipated that 10-15% of asymptomatic infants with cCMV will develop long-term sequelae. Hearing loss is the most well-known long-term complication [8,18].

1. Physical examination

- Small for gestational age (SGA) (birth weight ≤ 2 standard deviations for gestational age)
- Microcephaly (head periphery ≤ 2 standard deviations for gestational age)
- Petechiae or purpura (normally found within hours after birth and endure for several weeks)
- Blueberry muffin rash (intradermal hematopoiesis)
- Jaundice
- Hepatomegaly
- Splenomegaly

2. Neurological examination

- Microcephaly (head circumference ≤ 2 standard deviations for gestational age)
- Neurologic signs (lethargy, seizures, hypotonia, poor sucking reflex)
- Anomalies Distinguished Unexpectedly or Through Resulting Examination/Expert Assessment.

3. Laboratory results

- Anemia

- Thrombocytopenia (happens in the first week, however platelets frequently increment spontaneously after the second week) Leukopenia, isolated neutropenia
- Raised liver enzymes (alanine aminotransferase/aspartate aminotransferase) Conjugated hyperbilirubinemia
- Cerebrospinal fluid: Unusual cerebral fluid indices, positive CMV DNA
- Neuroimaging: Calcifications, periventricular cysts, subependymal, ventricular dilatation, pseudocysts, germinolytic cysts, white matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, lenticulostriatal vasculopathy
- Hearing test: Sensorineural hearing loss uni-or bilaterally
- Visual assessment: Chorioretinitis, retinal discharge, optic atrophy, strabismus, cataracts

cCMV infection is the main non-genetic reason for SNHL in children across studies. Among infants who foster CMV-related SNHL, hearing loss might be present at birth or may have postponed beginning, happening all through the first years of life. Around half of children with SNHL experience further deterioration or progression of their loss during adolescence, and the level of hearing loss might vary in up to half of the infants [19]. Therefore, it is vital that all infants with cCMV infection, independent of their clinical presentation at birth, get sequential audiological monitoring all through the first years of life to immediately distinguish possible SNHL to proceed with non-pharmacological mediations that can decrease the functional debilitation coming about because of hearing loss, altogether working on the receptive and expressive language and the social-emotional advancement of the impacted children [15,20,21].Moreover, cCMV is the main viral reason for neurodevelopmental delay, with an enormous extent of suggestive infants experiencing a few levels of psychomotor and mental handicaps and with visual weakness introducing in up to half of the symptomatic infants [7,22-26]. As many impacted children require critical continuous consideration and exceptional helpful and instructive administrations, the monetary burden related with congenital CMV infection is significant. Table (1)

Table1: Sequelae in Congenital Cytomegalovirus Infection[a]

	Symptomatic at Birth	[b] **Asymptomatic at Birth**
Hearing Loss	33%-40%	7%-10%
Characteristics of Loss		
Bilateral	67%-71%	43%-48%
Delayed Onset	18%-27%	9%-38%
Median age (range) of Delayed Onset loss	33months (6-197 months)	44months (24-182 months)
Progressive	18%-54%	20%-54%
Fluctuating	21%-22%	24%-48%
Severe-Profound Loss	75%	78%

Neurological Sequelae		
IQ <70	38%	0% b
Motor Abnormalities	22%	_
Seizures	18%	_

[a] (Dahle et al., 2000; Dreher et al., 2014; Goderis et al., 2016; Lopez et al., 2017) [b]Children with asymptomatic cCMV infection and developed SNHL by age 2 years had full-scale intelligence and receptive vocabulary scores that were lower than controls.

4. Maternal Screening

Taking into account that most of cCMV-infected children are born CMV IgG-seropositive women (non-primary maternal infection), as exhibited by populace review, global agreement discourages pre-birth screening of pregnant women since it can prompt nervousness, extra tests, and, surprisingly, unnecessary end of pregnancies [27-31]. Notwithstanding, a variable extent of pregnant women is tried for CMV IgG and IgM antibodies in Europe [32]. In Italy, around 40% of pregnant women are tried for CMV considering their gynecologist's or general specialist's suggestion [33]. Schooling of all pregnant women regardless of their serostatus and screening of all infants at birth addresses more compelling tools to forestall and recognize cCMV-diseased children [34].Despite the fact that thousands of children born each year are permanently disabled as a result of cCMV, the majority of pregnant women are unaware of CMV infection and its complications. Although there are knowledge gaps regarding CMV, awareness rates of 13–60 % are higher in Europe than in the United States [35–37].

Utilizing IgG and IgM serology, serologic testing can identify primary maternal infections: Only if CMV-specific IgM antibodies are detected, IgG avidity testing should be performed. IgM-positive results in addition to IgG avidity results can be used to distinguish between primary and non-primary CMV infections [38]. Low avidity suggests a recent infection, whereas high avidity for IgG early in pregnancy suggests a primary infection that occurred prior to conception [38,39]. However, early pregnancy testing may occasionally reveal a CMV IgG avidity result in the gray area, making parent consultation challenging. The risk of CMV transmission was higher in pregnant women with IgG avidity in the grey zone during the first trimester than in infants born after non-primary infection, according to a recent study [40], but further research is needed to confirm this finding.

Low levels of CMV-IgG antibodies in maternal serum samples in the absence of IgM may present a challenge for the clinician due to the possibility of a true positive or false positive result. Additional tests should be used to confirm the presence of CMV-specific antibodies in these women. Given that seronegative women can actually reduce their risk of acquiring a primary infection when properly counseled about hygiene measures, false-positive results are very concerning [41]. Serum samples with low IgG levels should not be subjected to CMV-IgG avidity testing because these samples may produce inaccurate IgG avidity results. A calculation for managing low certain IgG tests might be required, and without any a best quality level strategy, an obscure IgG serologic measure bring about a pregnant woman ought to be viewed as negative to guarantee that these women are relegated to the most noteworthy CMV risk group for pregnancy outcome [42].

5. Diagnosis of Fetal CMV Disease

Ultrasound imaging is valuable to predict the prognosis of fetal infection, despite the fact that it has poor sesitivity in prenatal diagnosis [43]. Amniocentesis to perform PCR for CMV DNA is the most ideal that anyone could hope to find prenatal diagnosis tool [44] since the infected fetus discharges urine containing the virus into the amniotic liquid. Two studies exhibited that on account of primary CMV infection, continuing levels of maternal DNAemia at the time of amniocentesis connected with a high gamble of CMV transmission to the fetus [45,46]. This technique has high sensitivity and specificity when performed following

20-21 weeks of gestation and 8weeks after assessed maternal seroconversion [1,47]. For this case, the prognostic assessment of fetal infection depends on imaging utilizing a mix of ultrasound and cerebral magnetic resonance imaging (MRI). Several investigations distinguished a residual hazard of hearing loss at birth while imaging assessment was viewed as negative [48-53].

5.1. Neonatal Screening

Since SNHL happens in roughly 10-15% of infants with asymptomatic congenital CMV infection and most children will encounter late-onset audiologic, neurologic, and developmental sequelae, neither physical assessment at birth nor newborn hearing screening address a dependable tool to recognize children in danger; in this manner, a reliable, quick, and conceivably not costly strategy to evaluate babies for intrinsic CMV infection is direly required. Early recognizable proof of these patients will permit them to be appropriately checked and to intervene during the acquisition of speech and language abilities [16]. The principal challenge in diagnosing CMV at the perinatal stage is to recognize congenital and postnatal infections. Any newborn with signs or symptoms demonstrative of intrauterine CMV infection ought to be tried [54]. Infected infants shed a lot of virus in saliva and urine; hence, these specimens are both valuable for the distinguishing proof of cCMV in infants. Various techniques have been assessed for use in the diagnosis of congenital CMV infection in light of saliva, urine, and dried-bloodspot (DBS) specimens got from newborns. Specifically, the usefulness of DBS specimens has been assessed since this sample is regularly acquired in all infants, in spite of the fact that for diagnostic purposes, this sample appears to have low sensitivity [55-64].

Virus isolation by culture from urine or saliva has for some time been the standard strategy for diagnosing cCMV infection. In any case, this strategy is costly, requires tissue cultures, isn't effectively amenable to automation, and, subsequently, can't be adjusted for large scale newborn screening. Since PCR displays high sensitivity in both saliva and urine tests [61,65], postnatal diagnosis of cCMV is ideally performed through real time polymerase chain reaction (PCR). Extra benefits of PCR assays are that assays are agreeable to automation, are minimal expense, are not impacted by storage and transport conditions, and don't need support of tissue culture facilities.Saliva specimens are really great for evaluating for cCMV; nonetheless, they are not regularly collected from neonates; thusly, an adjustment of framework is required before this strategy could be utilized for a large scope [42]. Clinicians ought to be cautious about testing saliva in the delivery room since this might build the gamble of false positives from cervicovaginal secretions; saliva ought to likewise be gotten at least 1 h after breastfeeding.The other valuable specimen in diagnostic congenital infection is urine on the grounds that infected newborns shed a lot of CMV in urine, yet its collection utilizing a pack might be complicated by a few variables, like lacking diuresis, loss of samples, or contamination. The utilization of different systems to gather urine, for example, cotton balls or filter cards in diapers, has not been assessed in enormous, populace-based screening programs and has not been compared and a highest quality level diagnostic technique [64,66].

In practically all countries, the screening program at birth has turned into a routine strategy to screen metabolic and genetic diseases in newborns, and DBSs on filter paper have been viewed as regarded as an intriguing and useful specimen for the detection of congenital CMV infection. Barbi et al. first showed that separating CMV DNA from DBS and successive amplification with real time PCR (RT-PCR) could consider the diagnosis of cCMV infection: the authors collected Guthrie cards from infants who were at that point tested positive for CMV infection with serological testing, tracking down a sensitivity up to 100% [67]; after four years, they affirmed their technique's high sensitivity and specificity, proposing that it could address a helpful option to viral culture [55]. From that point forward, the utilization of DBS as a diagnostic tool for cCMV has been generally studied, however in the literature, we have tracked down scarcely any steady studies. The CMV and Hearing Multicenter Screening (CHIMES) study by the Institute on Deafness and Other Communication Disorders (NIDCD) in 2010 was the main review that looked at CMV DNA testing by continuous PCR on Guthrie Card using a saliva-based viral culture technique and two distinct DNA extraction protocols [60] In general, the sensitivity of DBS RT-PCR went from 28.3% to 34.4%, depending upon the protocol. Both PCR protocols were 99.9% specific. These information's exhibited that RT-PCR analysis on DBS had low sensitivity for recognizing newborns with cCMV infection since up to 80% of infants with congenital CMV infections could be missed; in this way, it couldn't be suggested as a mass screening tools for the diagnosis of cCMV. A positive DBS PCR result could potentially identify infants with cCMV infection, as suggested by the high positive likelihood ratio (LR) for both PCR assays. Then again, the negative LR was not sufficiently low to exclude cCMV infection in newborns with a negative DBS PCR test.This survey assumed that with the continuous techniques, CMV testing with DBS RT-PCR is inappropriate for CMV screening, and its key application remains the review determination of cCMV disease in children with delayed onset sequelae. In these populaces, be that as it may, an adverse outcome doesn't exclude cCMV infection.

Various investigations can be found that depict higher awareness of perceiving CMV DNA by PCR using DBSs, from 45% up to 82%, on average [59,68]; the highest rate of recognition was depicted by Barbi et al., whose study arrived at a 100% sensitivity. All the above are review studies are retrospective or prospective studies directed on chosen populaces with known CMV infection [67]. One reason for the frustrating and variable sensibility of DBSs in the writing might be because of various specialized assays (DNA extraction technique, PCR protocol) [69] however is principally because of the way that newborns might have acquired the infection months before, and in this manner, up to 10-20% of children might have non-detectable viremia at birth [54,61]. Another issue concerning the utilization of DBS for the finding of cCMV infection is the way that DBS tests are at sometimes accessible for a brief period. Wang et al. announced that the storage times of Guthrie cards shift from 14 days to 18 years among 10 countries [70]. For specific areas, a few administrative changes in political decision ought to be considered to take into account longer storage of these samples. Despite all of this, a few authors gave proof of the great sensitivity of DBS for the retrospective diagnosis of cCMV in children developing neurological sequelae in the first few years of life. Besides, obviously some serious health issues (like SNHL, cortical development, pachygyria, cholestasis) would have been diminished because of DBS retrospective diagnosis [71,72]. At last, a few authors revealed the usefulness of DBS to recognize children in danger of developing long term sequelae [73,74].

A large prospective study on distributed in 2017 found that PCR of DBS had low sensitivity and specificity for recognizing infants with CMV-related hearing loss, at birth and at four years old [63]. In conclusion, the role of DBS PCR for testing CMV is more settled in retrospective diagnosis than in screening.The role of the viral load (VL) at birth has been as of late researched to decide if it could be a tumor marker of disease severity or could predict long term results; its part in distinguishing children who will develop complications in their first years of life has likewise been examined. The VL might be impacted by a several factors, for example, the timing of intrauterine infection, the PCR assay utilized, the quality and quantity of immunological response, and potential antiviral treatment [75].The biggest accessible dataset of blood VL at birth was gathered by Marsico et al. in 2018; their review planned to investigate the impact of antiviral treatment on viremia. Among symptomatic newborns, a higher viral load appears to correspond for certain markers of active diseases, like thrombocytopenia and transaminitis [75]. The scientists couldn't find a limit above which there is a more serious gamble of SNHL, and they likewise detailed that the individual VL doesn't anticipate the hearing outcome; in any case, children treated for quite a long time had a higher likelihood of hearing improvement assuming their viral load at birth was low. Besides, the review tracked down a pertinent relationship between higher VL at birth and CNS involvement. This was predictable with a prominent report that tracked down measurably important differences in quantitative PCR at birth among newborns with moderate-to-severe side effects and among those with the demonstrated neurological disease. Smilkovic et al., presumed that in spite of the fact that there is no VL cut off to recognize symptomatic and asymptomatic infants, patients whose standard viremia was over 100,000 copies/mL had a likelihood of having moderate-to-severe side effects that came to 100%[76]. Although the results came from small population studies with short-term follow-up , some other studies suggested that VL might predict late-onset SNHL[77,78].In summary, children with moderate-to-severe symptoms have a higher baseline VL than asymptomatic patients, according to the current literature. In order to better understand newborns with cCMV infection's risk of permanent sequelae, additional research into the role of viral load in infants with cCMV infection should be conducted.

6. Breastfeeding Neonates

Exclusive breastfeeding until at least six months postpartum, because breast milk (BM) is the best source of nutrition for newborns, especially those who are born prematurely [79]. Unfortunately, it is common knowledge that breast milk (BM) is not always safe, especially given the possibility of maternal viruses being present that can be shed and passed on to the newborn. In the beginning, CMV transmission to full-term infants was described as a natural immunization with few or no signs of disease [80,81]. BM-acquired infection can result in severe disease in premature infants [80]. Increased CMV transmission to the child may be linked to the elimination of a high viral load, early viral excretion, and prolonged breastfeeding [82,83]. As a result, it would be ideal to implement a method for removing CMV from BM without affecting its beneficial components in any way. The methods that are currently available are pasteurization, freezing, ultraviolet-C or microwave irradiation; They have varying effects on BM composition and differing levels of efficacy, and numerous studies are still required to fully clarify these implications [84].Colostrum, according to a recent study, should not be given without treatment and should not be considered safe [84]. Only newborns > 32 weeks of gestational age (GA) or weighing > 1000 g may receive fresh BM. If the mother tests positive for CMV-IgG, the BM should be pasteurized after the first three days of lactation for more preterm neonates. The true impact of CMV-

acquired infection in the neonatal period on the preterm outcome, particularly in terms of neurological sequelae, needs to be better understood in the future [85]. The approach for mother-to-child transmitted infections could be enhanced by cutting-edge methods like metabolomics [84].

7. Prevention

The development of an effective CMV vaccine faces a significant obstacle due to the complex nature of CMV protective immunity, which includes the risk of reinfection with genetically distinct viral strains and the possibility of reactivating an earlier infection. The ideal vaccines for congenital CMV infection should be able to boost the immune response in seropositive women to prevent reactivation or reinfection as well as protect seronegative women from the primary infection. Numerous CMV vaccine candidates are currently undergoing research, with vaccine candidates found in transplant recipients and animal models showing promising results. Despite these observations, it does not appear likely that a vaccine will be developed in the near future to prevent infection in the mother and child [86–89]. Education of pregnant women regarding sources of exposure and behavioural interventions to limit exposure to CMV remain the mainstay of interventions for the prevention of maternal infection and, consequently, congenital infection [16,90]. Table (2)

Table **2**: Steps recommended by the Centers for Disease Control and Prevention for reducing CMV exposure in pregnant women and thus reducing the risk of fetal infection [91].

- **Wash your hands often with soap and water for 15–20 seconds, especially after**
  - **changing diapers**
  - **feeding a young child**
  - **wiping a young child's nose or drool**
  - **handling children's toys**
- **Do not share food, drinks, or eating utensils used by young children**
- **Do not put a child's pacifier in your mouth**
- **Do not share a toothbrush with a young child**
- **Avoid contact with saliva when kissing a child**
- **Clean toys, countertops, and other surfaces that come into contact with children's urine or saliva**

8. Treatment

8.1. Antiviral Drugs

In recent years, significant advancements have been made in neonatal antiviral therapy for cCMV infection. Indication of treatment is constantly connected with symptomatic disease. Ganciclovir was the first treatment for congenital CMV infection that was looked at in studies 30 years ago. Later, oral valganciclovir was used. The use of antiviral medications in newborns with congenital viral infections must be balanced against the potential side effects. Kimberlin et al, published the results of a phase III, randomized, controlled trial of six weeks of ganciclovir versus no treatment in 2003 [92] to find out how from baseline to six months of follow-up, this drug affected changes in the brainstem-evoked response (BSER) (or, for patients with normal baseline hearing, normal BSER at both times).. From 1991 to 1999, 100 infants were chosen and randomized to receive ganciclovir intravenously at a dose of 6 mg/kg/dose twice daily for a month and a half or no treatment at all. The isolation of CMV from urine samples taken within the first month of life was confirmed for each study subject. In addition, the infants who were included had evidence of central nervous system disease, such as microcephaly, intracranial calcification, abnormal cerebrospinal fluid for their age, chorioretinitis, and/or hearing impairments, and their gestational age was greater than 32 weeks. Only 42 out of 100 infants received both a baseline and a 6-month BSER audiometric examination, indicating a high patient loss rate at follow-up.

21 babies (84%) out of 25 who got ganciclovir had improved hearing or kept up with normal hearing among control group between baseline and a half year, contrasted with ten out of seventeen infants,59 percent had not received any treatment.In addition,at six months, none of the ganciclovir recipients' hearing deteriorated, compared to seven (41%) of the seventeen people in the control group. In addition, 43 infants were able to participate in the one-year BSER hearing change evaluation in the best ear. At one year, compared to patients in the control group, 21% of those treated with ganciclovir experienced hearing loss. In conclusion, this randomized control trial (RCT) demonstrated that intravenous ganciclovir treatment for six weeks improved hearing outcomes at six months and prevented hearing loss, despite the high rate of follow-up loss. In an ensuing RCT, Oliver et al. [93] tried the adequacy of ganciclovir treatment in improving neurodevelopmental results at a 6months and 12months of age compared and patients who didn't get antiviral treatment. The population that was enrolled was the same as the one that Kimberlin et al. looked at. in the same comparative groups in 2003: infants who received 12 mg/kg/day of ganciclovir intravenously for six weeks compared to those who did not receive treatment. Denver II is a test were administered to subjects at the control visits at six weeks, six months, and twelve months of age during the previous clinical trial. The Denver II test, which is frequently used in pediatric care to assess developmental milestones, is broken down into four categories: personal/social, fine motor, language, and gross motor. However, because hearing loss is one of the most significant effects of congenital CMV infection, the category of language was excluded because the capacity to respond to particular stimuli is closely linked to hearing. Compared to infants who received no antiviral treatment, it was demonstrated that ganciclovir therapy may improve neurodevelopmental outcomes at six months and twelve months. The 12-month assessment revealed the greatest disparity in developmental outcomes between infants who received ganciclovir and those who did not. However, these results did not indicate that ganciclovir treatment could prevent all neurodevelopmental delays.

In neonates with symptomatic congenital CMV disease, a pharmacokinetic/pharmacodynamics study by Kimberlin [94] was published in 2008. It found that 16 mg/kg/dose of valganciclovir, the oral prodrug of ganciclovir, administered orally twice daily provided comparable systemic exposure and plasma concentration to the administration of intravenous ganciclovir. Similar to ganciclovir's toxic effects, valganciclovir caused moderate or severe neutropenia in 38% of infants. The fact that infants with congenital CMV infection were symptomatic at birth in all of these studies supported the hematologic toxicity and the possibility of carcinogenicity.The Collaborative Antiviral Study Group (CASG) conducted a phase III, randomized, placebo-controlled trial in 2008–2011 comparing 6 weeks of oral valganciclovir therapy with 6 months of intravenous ganciclovir therapy in light of the fact that intravenous ganciclovir treatment eliminates CMV from the urine but causes viremia to return within 2 weeks of stopping antiviral therapy [95]. 86 symptomatic infants with or without central nervous system involvement, such as microcephaly, intracranial calcifications, abnormal cerebrospinal fluid index, chorioretinitis, sensorineural hearing loss, or the detection of CMV DNA in cerebrospinal fluid. All of the infants were 30 days old or younger. Besides, eligible participants had a gestational age of 32 weeks or more. In fact, there are no randomized controlled studies that have treated neonates with cCMV infection under 32 weeks of gestational age. At the 6-month follow-up, the findings demonstrated that, in comparison to the improvements associated with shorter therapy of six weeks of oral valganciclovir, a longer duration of antiviral therapy did not further improve hearing function. However, hearing loss improved at 12 and 24 months in infants who received oral valganciclovir for 6 months (73% compared to 57% of the 6-week group).

At 12 and 24 months of follow-up, different audiologic outcomes did not correlate with the timing of starting valganciclovir within the first month of life. Using the third edition of the Bayley Scales of Infant and Toddler Development (Bayley-III), the group receiving six months of valgancyclovir therapy also had a better neurodevelopment score estimated at 24 months. In this study, it was shown that the occurrence of neutropenia was similar between the 6-week and 6-month groups (21% versus 27%). Notably, oral valgancyclovir was associated with a lower risk of developing neutropenia during treatment than was the risk associated with intravenous ganciclovir. Antiviral treatment for six months is thought to be an effective and well-tolerated option for symptomatic infants to improve long-term outcomes for hearing and neurodevelopment. The cited study [95] also looked into the differences between the two groups and how the blood viral load decreased during antiviral treatment. When compared to infants in the 6-month antiviral therapy group, infants with lower viral loads had better hearing function at 6, 12, and 24 months of follow-up, according to the analysis. On the other hand, oral valganciclovir did not correlate with a better endpoint at six weeks. Following this, Bilavsky et al., conducted a retrospective study in 2016 [96] found that receiving antiviral treatment for a year significantly improved hearing status in infants with symptomatic cCMV infection who began treatment within the first four weeks of life. According to the findings of this study, 64.9% of the ears with mild or moderate hearing loss at birth improved, while 6.5% of the affected ears deteriorated; 76% of those with improved ears were able to hear normally again. Indeed, even in

instances of serious hearing loss at birth, 40% of ears profited from antiviral treatment [96]. In addition, it appeared that the degree of impairment at birth was inversely correlated with the likelihood of hearing improvement. This study brought up a basic yet fascinating inquiry with respect to how antiviral treatment creates improvement rather than preventing the deterioration of SNHL. An answer has not yet been found in the literature. On the other hand, it is speculated that the virus's dynamic process of infection and inflammation continues after birth [96].

8.1.1 Toxicity of Antiviral Medications

The potential toxicity of antiviral medications must be addressed. Significant neutropenia is the main side effect; This typically occurs within the first month of treatment and is less prevalent with oral valganciclovir than with intravenous ganciclovir [94]. In RCTs comparing 6 months of treatment to 6 weeks of treatment, there was no evidence of increased toxicity. Additionally, risks associated with hospitalization and central line complications are eliminated when oral valganciclovir is administered. Hepatotoxicity and thrombocytopenia are two additional adverse effects that have been reported in up to 30% of ganciclovir-treated patients. The occurrence of these side effects might necessitate stopping therapy [97]. Because of the risk of short-term toxicity, regular clinical and blood tests are essential for monitoring patients. It is still unclear whether administering antiviral therapy for cCMV infection to infants is safe and without long-term side effects. In animal models, however, gonadal toxicity and cancer have been observed. To determine the possibility of this treatment strategy's long-term complications, additional research is required. To justify the risk versus benefit of treatment in asymptomatic infected infants with CMV-associated hearing loss, antiviral medications with improved toxicity profiles are required [98].

8.2. Vaccines

8.2.1 Live-Attenuated Vaccines

Live-attenuated vaccines are made by weakening infectious organisms so that they can't spread and elicit protective immune responses without infecting the host. Typically, these vaccines elicit a robust and persistent immune response due to their close resemblance to the natural infection. The first vaccines against hCMV that have been investigated are live-attenuated vaccines. An attenuated AD169 strain makes up V160, a live hCMV vaccine in which passages in endothelial cells restore PC expression [99]. The results in humans demonstrate the significance of V160, the first vaccine to express the PC, in eliciting potent neutralizing titers against viral infection [99,100]. Between November 2013 and March 2017, a placebo-controlled, randomized, double-blind phase 1 study (NCT01986010) [101] was carried out. A three-dose regimen was administered to healthy adults at day 1, month 1, and month 6. This evaluation confirmed that the neutralizing antibody and T cell response were induced by the V160 vaccine. In point of fact, antibody titers increased with each subsequent vaccination, with 100 percent of individuals being seropositive at month 7 and the majority remaining so at months 12 and 18. In addition, a cell-mediated immune response to hCMV was induced by the V160 vaccine, and this response grew with each dose. The majority of people reported only mild systemic side effects, most commonly headache and fatigue. Similar randomized, double-blind, placebo-controlled phase I studies were carried out to evaluate the V160 vaccine's immunogenicity and safety (NCT03840174) [102]. It included healthy male Japanese men between the ages of 20 and 64, but no results are yet available. Finally, a phase 2 clinical trial (NCT03486834) is currently in progress [103]. In this preliminary, solid, hCMV-seronegative women of childbearing age somewhere in the range of 16 and 35 years, who have direct exposure to young children at home or occupationally, and who consent to stay away from pregnancy during the treatment period, get 2 or 3 dosages of V160 antibody. Since the initial administration, they will be monitored for 36 months to assess the incidence of hCMV infection and adverse events.

8.2.2 Subunit Vaccines

Subunit vaccines only contain the antigenic components of the pathogen, particularly gB. Due to their limited components and non-replicating nature, these vaccines frequently require enhanced administration and adjuvants to increase their immunogenicity. In the early 1990s, Gonczol et al. described the ability of the purified virus envelope and the gA/Gb complex, which is comprised of glycoproteins gA, gp 55–116, p130/55, gB, and gcI, to elicit neutralizing antibodies and a cellular immune response in human volunteers [104]. Using immuno-adsorbent column chromatography-purified gA/gB, they administered vaccines to three naturally positive and two naturally negative human volunteers. The naturally seropositive individuals produced higher neutralizing antibody titers and temporarily elevated in vitro hCMV-specific lymphocyte proliferation responses following a single injection. After the third gA/gB injection, seronegative individuals developed briefly neutralizing antibodies. After the fourth injection, they

reappeared quickly and increased in title. The neutralizing antibody titers remained comparable to those of naturally seropositive individuals a year after the initial injection. After the second or third injection with the gA/gB preparation, the specific lymphocyte proliferation responses to hCMV in the initially seronegative individuals began and remained positive throughout the one-year observation period [134]. This finding demonstrated that gA/gB could serve as the basis for a subunit vaccine [104].

A phase I randomized, double-blind, placebo-controlled trial with a gB-based hCMV vaccine and an adjuvant, MF59, was conducted years after this discovery [105]. A powerful adjuvant for human vaccines based on an oil-in-water squalene emulsion is MF59. It is a powerful trigger of cell and humoral reactions to subunit antigens [106]. At 0, 1, and 6 months, adult participants in this study received the hCMV gB vaccine with MF59, the hCMV gB vaccine with alum, or a placebo. A particular subgroup received a fourth dose at twelve months. Two weeks after the third vaccine dose, subjects' levels of neutralizing antibody and antibody to gB were higher than those of seropositive control subjects. Additionally, the findings demonstrated that formulations containing MF59 were more immunogenic than those containing alum. Between 5 and 30 g of gB was the most effective dose. In addition, the antibody levels promptly increased at the fourth dose. The vaccine did not cause any serious side effects [105]. Other clinical trials in the 1990s demonstrated that the gB/MF59 vaccine was immunogenic and had acceptable side effect profiles. The difference in antibody responses between two different doses (five or thirty milligrams) and three different schedules (one, two, and three months) was the subject of a phase I study. 4, 6, and 12 months; or at 0, 1, and 6 months) of the hCMV gB vaccine in adults who are healthy and hCMV-seronegative. The vaccine caused the highest antibody titers when administered at 0, 1, and 6 months, and there was no significant difference in antibody production between the two doses [107].

In a 2002 open-label (at the time, observer blinded, and randomized) study, 18 children received either 20 g of hCMV gB/MF59 or a control hepatitis A immunization at 0 days, 1 month, and 6 months. The gB/MF59 vaccine was found to be highly immunogenic and to be well tolerated by children [108].The primary stage 2 preliminary was led from August 1999 to January 2010 in hCMV-seronegative women in the span of 1 year after delivery (ClinicalTrials.gov number, NCT00125502) [109]. They compared a recombinant hCMV envelope gB immunized with MF59 adjuvant to a placebo in this stage 2 preliminary placebo-controlled, randomized, double-blind study. Three doses of the hCMV antibody (234 subjects) or placebo (230 subjects) were given at 0, 1, and a half year to hCMV-seronegative women. The outcomes showed that the immunization group had less diseases during a 42-month period than the placebo group. Avaccine efficacy was 50%. There were more nearby and fundamental responses in the antibody group than in the placebo group. This preliminary inferred that the gB/MF59 immunization can possibly diminish maternal and cCMV infection [109]. In a review distributed in 2011, the gB/MF59 immunization was tried in hCMV-seropositive women, to support the mother's immunity to hCMV and perhaps decrease cCMV infections [110]. This study exhibited that both CMV-specific antibody and CD4+ Lymphocyte reactions can be helped after immunization with a hCMV gB/MF59 antibody in women with chronic hCMV disease. Further investigations are expected to assess whether these supported reactions might prevent vertical transmission of hCMV.

In a stage 2 randomized, placebo-controlled preliminary (NCT00299260), adults with SOT were given the gB/MF59 vaccine from August 2006 to September 2011 to see if it could prevent hCMV end-organ disease. At 0, 1, and a half year, they managed 70 seronegative and 70 seropositive patients with either gB/MF59 immunization or placebo. Both seronegative and seropositive recipients of the antibody had significantly higher GB antibody titers than the placebo group. gB antibody titers were inversely correlated with the duration of viremia in those who developed it following transplantation. The number of days of ganciclovir treatment and the duration of viremia in seropositive patients and seronegative donors were decreased in vaccine recipients [111]. At last, a randomized, double blind, placebo treatment controlled, stage II review surveyed the safety and efficacy of the hCMV gB/MF59 immunization in healthy adolescent females (ClinicalTrials.gov Identifier: NCT00133497). Roughly 400 hCMV-seronegative girls somewhere in the range of 12 and 17 years old got gB/MF59 or placebo treatment at 0, 1, and a half year. The immunization prompted gB antibodies in all immunization recipients after 3 doses. Overall, 48 hCMV infections were distinguished (21 in the antibody group, 27 in the placebo treatment group). Immunization adequacy was 43%. They inferred that the gB/MF59 antibody was protected and immunogenic, albeit the adequacy didn't arrive at traditional degrees of importance and was not adequate to proceed with the advancement of this immunization [112].

8.2.3 Virus Infection Vectored Vaccine

Virus vectored vaccines utilize a carrier vector to move hCMV antigens and induce immune reaction against hCMV likewise because of the adjuvant impact, which is essential for the vector. The presence of previous of anti-vector immunity or its potential improvement could address an issue for this kind of vaccine. We portray the hCMV vector-based up-and-candidate vaccines tried

in clinical preliminaries. Attenuated poxvirus changed Vaccinia Ankara (MVA) is a viral-based immunization with an ideal safety profile and fit for inciting areas of strength for a reaction against recombinant antigens [113]. By creating an MVA encoding three immunodominant hCMV antigens—pp65, IE1-exon4, and IE2-exon5—City of Hope produced Triplix, an additional hCMV immunization applicant [113]. Triplix was first assessed in a stage 1 preliminary in 24 healthy adults, with or without immunity to hCMV. Three escalating dose levels of the immunization were assessed, every one tried in a companion of 8 subjects who got the antibody and an identical booster dose 28 days later. hCMV serological status was kept an eye on days 0, 180, and 360. The review established that vaccinations were safe with no dose restricting toxicity levels, no serious unfavourable events, and just mild local and systemic reactogenicity. LaRosa et al. showed critical and dependable developments of hCMV-specific Lymphocytes, with potential for viremia control, additionally in hCMV-seronegative subjects and in adults who recently got smallpox immunization, along these lines demonstrating that Triplix is safe and exceptionally immunogenic [113].

Consequently, a multicenter, randomized, and placebo treatment-controlled stage 2 clinical trial was started in 2015, enlisting in danger, hCMV-seropositive HSCT recipients (NCT02506933). Patients got Triplix or placebo treatment on day 28 and day 56 after HSCT and went through a1-year follow up [114]. The essential results were hCMV reactivation, hCMV viremia requiring antiviral treatment, end-organ disease, non-relapse mortality, and serious GVHD. This preliminary affirmed that Triplix produces hCMV-specific immune reactions: the gamble for a significant hCMV event during the initial 100 days after transplant was decreased by half in patients who got Triplix. Compared to patients receiving a placebo, recipients of the Triplix vaccine had significantly higher levels of hCMV-specific white blood cells and fewer hCMV reactivations. [114]. Following the progress of this preliminary, in 2018, City of Trust chose to advance another review, enrolling contributors of hCMV-seropositive HSCT beneficiary (NCT03560752) [115]. This phase 2 as yet continuous preliminary includes donors getting one Triplix dose between days 60 and 10 preceding G-CSF mobilization to foster a hCMV-specific Lymphocyte reaction; should this immunity be moved to the recipients, they could possibly prevent hCMV viremia and lessen the probability of hCMV disease before antiviral prophylaxis. Possible administration of the vaccine likewise to the recipients will be explored to protection the assurance period as long as 200 days after transplantation [114]. Triplix is presently likewise under assessment in the pediatric populace: a phase1/2 clinical review is continuing to decide the ideal dose and the protective impact of this immunization in hCMV-seropositive children getting an allogeneic HSCT (NCT03354728) [116]. Triplix could likewise in the long run be utilized in patients who get *Society of Toxicology* (SOT) and City of Trust is arranging studies on in this populace also [117,118].

Using the lymphocytic choriomeningitis infection to express the gB and pp65 antigens, Hookipa Pharma (New York, NY, USA) developed the vaccine known as HB-101. This infection is pathogenic to rodents, and it very well may be utilized as a vector fit for creating both antibody and cell reactions [117]. In 2016, a placebo controlled, double blind phase I preliminary occurred, to assess the safety and the immunogenicity of three administrations of HB-101 at three different dose levels in healthy adults (NCT02798692) [119]. HB-101 was very much endured and induced hCVM-specific cell reactions, primarily pp65-explicit CD8 Lymphocyte, and neutralizing antibodies creation in many subjects. The researchers noticed an absence of vector-killing neutralizer reactions, which ought to help HB-101 functioning [120]. These outcomes prompted a randomized, placebo controlled, phase 2 preliminary to assess the safety and efficacy of HB-101 in hCMV-seronegative patients getting a kidney transplant from seropositive donors. This preliminary is really enlisting patients. (NCT03629080) [121].

8.2.4 Chimeric Peptidic Vaccines

Chimeric vaccines are recombinant vaccines produced by substituting genes encoding for target antigens from the pathogen in a safe yet firmly related organism. Chimeric vaccines have generally been studied for the protection of HSCT recipients [122]. It has been established that the primary motivating antigen that initiates the T cell immune natural reaction is the abundant tegument protein pp65. [123]. For sure, pp65 is one of the main targets for HLA class I-confined CD8+ cytotoxic T lymphocytes (CTLs). Specifically, pp65495-503, a CTL epitope inside the pp65 protein that is limited to the high-frequency HLA A*0201 allele, is viewed as highly protective because of its low sequence variability among viral isolates and can extend human pp65-explicit memory CTLs [124,125]. The early and late expression of pp65 by hCMV-infected cells makes it an ideal vaccine target. [126]. Besides, it was noticed that connecting pp65 CTL and a T helper epitope notably upgraded the immunogenicity of these immunizations. Consequently, this CTL epitope was combined to a widespread T-helper epitope, either a synthetic pan HLA-DR epitope (PADRE) or a natural tetanus (Tet) sequence, regardless of CpG 7909, a toll like receptor 9 (TLR9) synthetic oligonucleotide antagonist, and the combination showed positive immunogenicity profiles [127]. CpG7909, which is a significant receptor expressed in immune system cells, further builds the action of the immunization, allowing a decrease of its dosage [127].

Using HLA-restricted CTLs epitopes for a vaccination would clear out the issues concerning live-constricted or recombinant live popular immunization in HSCT beneficiaries. Also, it was shown that hCMV complexities in HSCT patients were related with low degrees of pp65 CTLs, while protection from reactivation was related with high levels [128].

8.2.5 Vaccine of Enveloped Virus Like Particles

This sort of antibody utilizes supra-molecular protein structures that mimic the genuine infection however don't contain the viral genome. A vaccination containing the extracellular space of hCMV gB combined with the transmembrane and cytoplasmic spaces of vesicular stomatitis infection G protein (gB-G eVLPs) was created by VBI Immunizations Inc. (Cambridge, MA, USA) [129]. It was tested in a Phase 1 placebo-controlled, randomized, observer-blind clinical trial (NCT02826798) [130]. The objective of the study was to evaluate the immunogenicity and safety of four dose formulations of VBI-1501 in healthy hCMV-seronegative volunteers, with or without alum. After two doses, especially in patients who received vaccine with adjuvant, titers of antibodies increased. Antibodies against fibroblast cells were viewed as in 100 percent of recipients, and against epithelial cells in 31%. There were no security issues and the vaccine were found to be immunogenic at very low doses [117,130].

8.2.6 Plasmid-Based DNA

Vaccines Plasmids (circular DNA vectors) serve as versatile platforms on which one or more antigens can be incorporated to elicit antigen-specific immunity in plasmid-based DNA vaccines.The bivalent hCMV DNA vaccine VCL-CB01, also known as ASP0113, consists of two plasmids encoding pp65 and gB, VCL-6368 and VCL-6365; it is joined with two adjuvants, poloxamer CRL1005 and benzalkonium chloride [131,132]. In a 2008 phase 1 clinical trial, 44 healthy adult subjects received either 1- or 5-mg vaccine doses over a 0-, 2-, and 8-week period, or 5-mg vaccine doses over a 0-, 3, 7, and 28-day period. The vaccine was generally well tolerated, and there were no serious side effects. The immunogenicity of 45.5% of hCMV-seronegative subjects and 25% of hCMV-seropositive subjects was documented through week 16 of the study, and 68.1% of hCMV-seronegative subjects still had memory at week 32 [126].

108 adult recipients of allogeneic HSCT (*hematopoietic stem cell transplantation)* who were positive for hCMV participated in the multicenter, randomized, double-blind, placebo-controlled phase 2 trial of ASP0113 (NCT00285259). Subjects were randomly assigned to receive 5-mg doses of the vaccine or a placebo, and subsequent to transplantation, approximately 1, 3, and 6 months later. The vaccine was well tolerated, and vaccine recipients had higher frequencies of pp65-specific interferon-producing T cells and significantly lower viral load endpoints than placebo recipients; However, the need for hCMV antiviral therapy was not significantly reduced in comparison to placebo [133]. The primary and secondary endpoints of a global phase 3 trial in HSCT recipients were established based on this trial's findings.

As tellas Pharma Global Development, Inc. (Tokyo, Japan) and Vical collaborated on the design of the global phase 3 trial (HELIOS) of ASP0113 [134]. It was a placebo-controlled, randomized, double-blind study of ASP0113 in allogeneic HSCT recipients who were positive for hCMV. 500 individuals were randomized to get either 5 mg of ASP0113 or a placebo treatment when 14 to 3, 14 to 40, 60, 90, and 180 before the transfer (day 0). The essential adequacy endpoint of this preliminary was in general mortality at one-year post-transplantation. ASP0113's safety was also monitored in HCT recipients. The percentage of participants who had hCMV viremia and required hCMV-specific antiviral therapy one year after transplant were secondary outcomes. However, the Phase 3 HELIOS clinical trial's primary and secondary endpoints were not met by ASP0113 because there was no significant increase in overall survival or decrease in hCMV end-organ disease. The immunization was by and large all around endured, with infusion site responses being the most generally revealed unfavourable occasion.

The efficacy, safety, and immunogenicity of ASP0113 were evaluated in hCMV-seronegative kidney transplant recipients from hCMV-seropositive donors in a phase 2 randomized, double-blind, placebo-controlled study [135] (NCT01974206) that lasted from November 2013 to November 2020. Altogether, 150 transfer recipients were randomized (1:1) to get 5 dosages of ASP0113 (5 mg) or placebo on days 30, 60, 90, 120, and 180 post-relocate; they likewise got prophylactic valganciclovir/ganciclovir 10-100 days post-relocate. The extent of relocate recipients with hCMV viremia 1000 IU/mL from day 100 to one year after the principal antibody infusion was the essential endpoint. The primary endpoint did not differ between the ASP0113 and placebo groups in a way that was statistically significant, so it did not prevent hCMV viremia [136].VCL-CT02, an immunotherapeutic trivalent plasmid DNA-based vaccine, was the subject of only one phase 1, single-centre, randomized, open-label trial (NCT00373412) [137]. It was given on days 1, 7, and 14, then the Towne hCMV Vaccine (Towne) was given. Twelve healthy, hCMV-negative participants were enrolled and assigned to receive either Towne alone or VCL CT02 followed by Towne. During

the 252 days following the Towne challenge, both T cell responses to hCMV antigens and antibody to hCMV gB were measured. The outcomes have not yet been made available.

8.2.7 RNA-Based Vaccines

An RNA vaccine causes the immune system to respond to the pathogen's correspondent antigen by using a synthetic copy of the pathogen's messenger RNA (mRNA). Non-replicating mRNA, which only contains antigens of interest, or self-amplifying mRNA, which also contains proteins necessary for RNA replication, can be used to create RNA vaccines. The co-formulation of the molecule into lipid nanoparticles, which help the RNA strands get into the cells and protect them, is how mRNA is delivered. Numerous successful preclinical studies of hCMV RNA-based vaccines have been conducted. The ability to encode any antigen and deliver multiple antigens in a single vaccination is a major advantage of this method [138]. The development of effective vaccines for a wide range of human diseases, including coronavirus disease 2019, presents new opportunities through the utilization of an RNA vaccine platform [139]. gB and a pp65-IE1 fusion antigen were both prepared in a cationic nano emulsion delivery system for the initial synthetic, self-amplifying mRNA vaccine. Brito and colleagues demonstrated that every mouse, rat, rabbit, and non-human primate tested developed a potent antibody and T cell response after receiving two intramuscular doses [140].

Modified mRNAs encoding gB and PC, both contained in lipidic nanoparticles, were the second candidate tested in a preclinical study. Potent and long-lasting neutralizing antibody titers were produced by immunization of mice and non-human primates. Another mRNA vaccine expressing the immunodominant hCMV T cell antigen pp65 was developed in order to study the hCMV T cell response. In mice, organization of pp65 immunization along with PC and gB prompted a powerful Lymphocyte explicit reaction that was most noteworthy in the event of successive administration of pp65 alone followed by immunization with PC + gB+ pp65 [141]. The hCMV vaccines mRNA-1647 and mRNA-1443 were examined in a phase I randomized, placebo-controlled, dose-ranging trial sponsored by Moderna (NCT03382405) [142]. The first one contains mRNAs for pp65, while the second one contains mRNAs for gB (1 mRNA) and PC (5 mRNAs). In adults between the ages of 18 and 49, they tested its safety and ability to elicit an effective antibody and T cell response. After the third vaccination with mRNA-1647 in the 30-, 90-, and 180-g dose cohorts, the company reported positive interim safety and immunogenicity data in March 2020. Based on these hopeful outcomes, Moderna fabricated a stage 2 review surveying the wellbeing and viability of mRNA1647 in 252 either hCMV-seronegative or -seropositive solid grown-ups (NCT04232280) [143]. In three shots (0, 2, and 6 months), the vaccine is given at three dose levels (50, 100, and 150 mg). The same company is getting ready to launch a Phase 3 global, randomized, observer-blind, placebo-controlled study to see if mRNA-1647 is effective against primary hCMV infection in women who are pregnant [144].

8.2.8 Peptide Vaccines

Short peptide fragments are used in peptide vaccines to elicit highly specific immune responses.In a new forthcoming stage I preliminary (CMVPepVac study: EudraCT No. RCHD-CMV-1001 2012-002486-35; Prior to renal transplantation, a CMVpp65 peptide vaccine (ISRCTN11842403) was tested on ten hCMV-negative end-stage renal disease patients. Subcutaneously, four times every two weeks, the highly immunogenic nonamer peptide NLVPMVATV, which was derived from hCMVpp65, was combined with imiquimod (AldaraTM) as an adjuvant in a water-in-oil emulsion (MontanideTM). Both the clinical course and the immune responses were monitored. Except for local skin reactions, this vaccination was well tolerated, and no serious adverse events were observed. Half of the patients had a resistant reaction and 40% introduced hCMV-explicit CD8+ Immune system microorganism reactions. In contrast to nonresponse’s, all responders reactivated hCMV in the 18 months following transplantation. The correlation between hCMV-specific T cell reactivity and vaccine response necessitates additional multi-centre studies with larger patient cohorts due to the small number of patients [145].

8.3 Efficacy of hyperimmune globulin in clinical trials

A non-randomized trial using HIG at a dose of 100U per kilogram intravenously monthly reported a significant decrease of fetal transmission from 40% in untreated women to 16% in treated ones (146). These results were not confirmed by a double-blind randomized, placebo-controlled trial in 124 pregnancies with primary CMV infection (147): HIG given monthly at the same dosage than previously was followed by a 30% transmission rate that was not significantly lower than 44% observed with placebo (NaCl). In addition, there was an increase, although not significant, of premature babies, in the HIG group. Another placebo controlled RCT trial was conducted in the United States using the same criteria but was designed to include 800 women. The trial

was stopped for futility at interim analysis of the first 399 cases showing transmission rates of 22.7% and 19.4% in the HIG and placebo groups respectively. The rates of preterm birth were similar in both groups (12.2% V.8.3%) (148).

The debate on the use of HIG was however revived on the ground of the pharmacokinetic of CMV HIG showing that CMV IgG have a shorter half-life of about 11 days in maternal blood compared to 22 days as previously reported (149,150). Biweekly administration of HIG might therefore be more efficient than monthly administration as used in previous trials (146–148). A non-randomized Phase I study reported that bi-weekly administration of a 200 U HIG decreased maternal-fetal transmission compared to a historical cohort (7.5% v 35%) in the context of systematic serology screening in pregnancy (151). In addition to the higher dosage of HIG, the authors of the latter study brought-up the issue of the importance of including only cases with a very recent primary infection. This could prove important since maternal and therefore placental viremia precede the appearance of IgM and IgG by one week. Those parameters were indeed controlled in the animal studies, but not in the 2 RCTs conducted to date. Therefore, although HIG seem safe in pregnant women, their efficacy has not been demonstrated in clinical practice and the potential impact of the dosage and timing of administration remains to be established.

III. Conclusion

cCMV infection is the first non-genetic cause of SNHL in children and a significant cause of other neonatal morbidities. There are still some unanswered questions, despite the promising developments in neonatal diagnosis and antiviral therapies for cCMV over the past few years. Even though there is a great deal of interest in this area of research and numerous clinical trials are currently taking place to develop a vaccination for pregnant women, there are still no preventive interventions other than behavioural measures during pregnancy. Since PCR does not require costly tissue culture, we currently recommend diagnosing cCMV infection using a PCR assay in blood, urine, and saliva rather than culture; It is associated with a relatively low cost and a faster test. A general screening test utilizing DBS, a standard example gathered upon entering the world, has been proposed yet requires further examination and improvement for broad use. We repeat the significance of appropriate storage of the specimen taken at birth to allow us to recognize an intrinsic disease from a postnatal infection, attributable, for example, to diseased BM from a seropositive mother [64,98]. Asymptomatic infants do not appear to benefit from antiviral treatment at this time. In addition to all of the potential benefits, antiviral therapy must consider known risks like neutropenia and/or thrombocytopenia as well as potential risks like gonadal toxicity and carcinogenicity that have been observed in animal models. For cCMV infection, oral valganciclovir (16 mg/kg/dose, twice daily) is actually our recommendation for a 12-month course of treatment. The viability and tolerability of this treatment choice have demonstrated successful for hearing and neurodevelopmental long-term results. Congenitally infected neonates with symptomatic disease at birth, such as microcephaly, intracranial calcifications, abnormal cerebrospinal fluid index, chorioretinitis, or sensorineural hearing loss, are only eligible for the treatment with valganciclovir. Due to a lack of studies, antiviral treatment is not typically recommended for neonates with the mildly symptomatic disease at birth, infants under 32 weeks of gestation, or infants older than 30 days. However, since these populations represent the vast majority of neonates and infants with cCMV infection and are at risk of developing late-onset sequelae, a biomarker that is able to predict long-term sequelae should also be discovered in order to justify initiating treatment and lessen the burden of CMV-related complications.

IV. Conflict Of Interest

All authors declare no conflicts of interest.

V. Authors Contribution

Authors have equally participated and shared every item of the work.

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