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# Treatment of Congenital Cytomegalovirus and Ganciclovir Therapeutic Drug Monitoring in Twin Preterm Infants

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Congenitally acquired cytomegalovirus (CMV) infection is the most prevalent congenital infection worldwide and the most frequent cause of acquired sensorineural hearing loss. The burden of the disease is even more important in premature and very low birth weight infants. However, few data exist on the treatment with intravenous ganciclovir and oral valganciclovir in this vulnerable population. We report the case of twins congenitally infected with CMV and born prematurely at 27 weeks' gestation. Treatment regimens were initially individualized for their prematurity and renal function, and then adjusted with therapeutic drug monitoring (TDM) to adapt to their continuously evolving physiologic maturation. As infants were aging, the plasmatic half-life of ganciclovir slowly decreased to term infant values around 10 weeks of chronological age, or 37 weeks of postmenstrual age. Results for blood polymerase chain reaction tests became negative and long-term follow-ups were satisfactory in both twins. The limited data for infants born before 32 weeks of gestation or at less than 1200 g and evolution of ganciclovir pharmacokinetic parameters justify the use of TDM in these settings.

**ABBREVIATIONS** AUC, area under the curve; CMV, cytomegalovirus; cCMV, congenitally acquired cytomegalovirus; CSF, cerebrospinal fluid; DOL, day of life; ELBW, extremely low birth weight; HPLC, high-performance liquid chromatography; IV, intravenous; NEC, necrotizing enterocolitis; PCR, polymerase chain reaction; SNHL, sensorineural hearing loss; TDM, therapeutic drug monitoring; TTTS, twin-to-twin transfusion syndrome; VLBW, very low birth weight

**KEYWORDS** congenital infection; cytomegalovirus; ganciclovir; premature infant; therapeutic drug monitoring; valganciclovir; very low birth weight infant

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## Introduction

With an overall prevalence at birth of up to 1%, human cytomegalovirus (CMV) is the most frequent congenital infection in newborns.[1] It can be acquired *in utero*, leading to congenital infection, or postnatally.[2,3] Distinguishing between congenital and postnatal acquisition of CMV in infants, while sometimes challenging, is essential to provide appropriate treatment.[3] About 10% of infected newborns present with clinical manifestations at birth, such as petechiae, jaundice, hepatosplenomegaly, and microcephaly.[3,4] With hearing deficit in up to 65% of infected and symptomatic newborns, congenitally acquired CMV (cCMV) is considered the most frequent cause of acquired sensorineural hearing loss (SNHL) worldwide.[3–5] The burden of cCMV is even more important in premature and very low birth weight (VLBW) infants, because it is more likely to be associated with abnormal neuroimaging, neurodevelopmental delay, and SNHL.[6]

Treatment with intravenous (IV) ganciclovir 6 mg/kg/dose every 12 hours for 6 weeks decreases the risk of CMV-related SNHL.[4] In neonates, oral valganciclovir 16 mg/kg/dose every 12 hours leads to comparable systemic exposure achieved with IV ganciclovir 6 mg/kg/dose every 12 hours.[7] A 6-month treatment with valganciclovir was shown to be modestly superior to a 6-week regimen in improving the hearing and developmental outcomes for these patients.[8] Although these regimens have been described as safe and efficient for children born as early as 32 weeks of gestation, data are lacking concerning pharmacokinetics, efficacy, and safety in more preterm newborns, except for few case reports.[9,10]

We present the case of 2 preterm twin infants with cCMV for which we performed therapeutic drug monitoring (TDM), measurements of CMV viral loads, and close monitoring of adverse effects. Following these cases and our review of literature, we propose a model of treatment and monitoring for preterm infants congenitally infected with CMV.

**Table 1.** Infant Characteristics

| Characteristic | Infant 1 | Infant 2 |
|---|---|---|
| Birth weight (Z-score) g | 1100 (0.47) | 980 (−0.12) |
| Head circumference (Z-score) cm | 26 (0.67) | 25 (−0.06) |
| Initial blood viral load (log10) | 3090 (3.49) | 4169 (3.62) |
| Initial cerebrospinal fluid viral load (log10), copies/mL | 0 (0) | 832 (2.92) |
| Serum creatinine at treatment initiation, mg/dL | 0.79 | 1.26 |
| Suspected treatment-related toxicity | Transient neutropenia at 2 mo (no treatment required) | Neutropenia (requiring 2 doses of g-CSF) |

*g-CSF, granulocyte-colony stimulating factor*

## Case

The infants were 2 male monochorionic diamniotic twins born at 27[3] weeks of gestation from a healthy 22-year-old mother. Stage 1 twin-to-twin transfusion syndrome (TTTS) with polyhydramnios was treated by amniocentesis at 26[5] weeks. The infants were born by cesarean delivery following preterm labor and breech position of infant 2. Two intramuscular doses of betamethasone 12 mg at 24-hour intervals were administered 6 and 7 days prior to birth. The day after delivery, maternal serologic testing was positive for CMV immunoglobulin G (immunoglobulin M test was not performed).

The first twin was diagnosed as the donor twin because of oligohydramnios. He was found to have mild leukopenia (7.1 × $10^9$/L) and thrombocytopenia (65 × $10^9$/L) at birth. Liver enzymes remained normal throughout his hospitalization and physical examination did not reveal any hepatosplenomegaly. Urinary polymerase chain reaction (PCR) findings were positive for CMV on day of life (DOL) 4. While blood PCR demonstrated active CMV infection, viral load was negative in the cerebrospinal fluid (CSF) (Table 1). CMV workup also included cerebral ultrasonography, which was normal. Given concerns about immaturity of renal function, possible additional renal dysfunction related to the TTTS status, and lack of data regarding the use of ganciclovir in infants born before 32 weeks of gestation, a decreased dose of ganciclovir 3 mg/kg/dose every 24 hours, administered by IV infusion via a central line over 1 hour, was initiated at DOL 4. Using TDM (see below for specifics), plasma ganciclovir areas under the curve (AUCs) were estimated and served for ganciclovir dose adjustments (Table 2). Blood CMV PCR load decreased rapidly after treatment initiation and findings were negative at DOL 33 (Table 2). The clinical course of this infant was free of any CMV-related complications and IV ganciclovir was switched to oral valganciclovir at 12 mg twice a day (7.4 mg/kg/dose) given simultaneously with enteral feeding (Valcyte oral solution, Hoffmann-La Roche Ltd, Missisauga, Ontario, Canada) at DOL 33. Hearing screening test performed at 34 weeks of postmenstrual age was normal. The valganciclovir dose was adjusted according to TDM throughout hospitalization. At discharge, the 16 mg/kg/dose every 12 hours recommended for term infants was prescribed to complete a 6-month treatment course.

The second twin was diagnosed as the recipient because of polyhydramnios and hypertrophic cardiomyopathy. His weight was suggestive of intrauterine growth retardation in regard to his recipient status (Table 1). He had leukopenia (5.5 × $10^9$/L) and severe thrombocytopenia (93 × $10^9$/L) for which a platelet transfusion was given at DOL 3. No hepatosplenomegaly was identified on clinical examination and liver enzymes were initially normal. Echocardiography revealed biventricular hypertrophy and right ventricular pericardial fluid collection. CMV PCR testing of urine, blood, and CSF was positive on DOL 4. Owing to hypotension and increased serum creatinine (1.26 mg/dL), the antiviral treatment was not initiated immediately. Upon improvement of renal function and blood pressure following fluid resuscitation and adjustment of maintenance fluid intake, ganciclovir was started at 3 mg/kg/dose administered every 24 hours by IV infusion via a central line over 1 hour on DOL 5 and adjusted by using TDM (Table 2). Cerebral ultrasonography revealed hyperechogenicity of the choroid plexus and a discrete white matter bilateral hyperechogenicity, but no calcifications. At DOL 10, pneumatosis was noted on plain abdominal x-ray and a diagnosis of grade II necrotizing enterocolitis (NEC) was made. Medical treatment was started for NEC, including bowel rest and antibiotics (ampicillin, gentamicin, and metronidazole). His condition further worsened, and ganciclovir was suspended at DOL 14 secondary to profound thrombocytopenia (25 × $10^9$/L) and neutropenia (1 × $10^9$/L). Given that quantitative CMV PCR in blood revealed an increasing viral load, ganciclovir was reinstated on DOL 16 along with 7 mcg (5.5 mcg/kg/dose) of granulocyte-colony stimulating factor IV given over 5 to 10 minutes via a central line (commercial solution of 300 mcg/mL diluted in D5W

**Table 2.** Exposure Parameters, Viral Loads, and Hematologic Laboratory Results During Ganciclovir and Valganciclovir Treatment*

| | AUC 1 | AUC 2 | AUC 3 | AUC 4 | AUC 5 | AUC 6 | AUC 7 | AUC 8 | AUC 9 |
|---|---|---|---|---|---|---|---|---|---|
| Infant 1 | | | | | | | | | |
| DOL, days | 7 | 14 | 20 | 28 | 35 | 41 | 56 | 71 | 77 |
| Postmenstrual age, wk | 28[3] | 29[3] | 30[2] | 31[3] | 32[3] | 33[2] | 35[3] | 37[4] | 38[4] |
| Medication | GCV | GCV | GCV | GCV | V-GCV | V-GCV | V-GCV | V-GCV | V-GCV |
| Dose, mg/kg | 3.0 IV q24 | 2.4 IV q18 | 2.1 IV q18 | 2.2 IV q12 | 7.5 PO q12 | 6.8 PO q12 | 5.2 PO q12 | 5.8 PO q12 | 7.8 PO q12 |
| Plasma GCV peak/trough concentrations, mg/L | 3.32/0.85 | 3.6/0.83 | 2.74/0.61 | 2.53/0.79 | 2.24/1.37 | 3.73/0.99 | 2.25/0.5 | 2.18/0.11 | 2.68/0.3 |
| Estimated $AUC_{0-12\ hr}$, mg·h/L | 22.0 | 28.1 | 20.8 | 20.3 | 22.6 | 28.1 | 16.4 | 14.2 | 14.8 |
| Estimated plasma GCV half-life, hr | 11.7 | 7.7 | 7.6 | 6.4 | 11.4 | 4.6 | 4 | 2.1 | 2.8 |
| Blood CMV viral load (log), copies/mL | 3090 (3.49) | 871 (2.94) | 478 (2.67) | 0 | 0 | - | - | - | - |
| Creatinine, mg/dL | 0.74 | 0.59 | 0.51 | - | - | 0.42 | 0.43 | 0.37 | 0.37 |
| Platelet count, $\times 10^9$/L | 126 | 225 | 124 | - | - | 373 | 269 | 193 | 285 |
| Neutrophils, $\times 10^9$/L | 2.9 | 3.8 | 2.9 | - | - | 1.8 | 1 | 0.8 | 1.2 |
| Infant 2 | | | | | | | | | |
| DOL, days | 10 | 20 | 28 | 36 | 42 | 48 | 55 | 69 | 84 |
| Postmenstrual age, wk | 28[6] | 30[2] | 31[3] | 32[4] | 33[3] | 34[2] | 35[2] | 37[2] | 39[3] |
| Medication | GCV | GCV | GCV | GCV | GCV | GCV | GCV | V-GCV | V-GCV |
| Dose, mg/kg | 2.5 IV q24 | 2.3 IV q24 | 2.1 IV q24 | 1.9 IV q18 | 2 IV q12 | 2.8 IV q12 | 2.7 IV q12 | 7.1 PO q12r | 9 PO q12 |
| Plasma GCV peak/trough concentrations, mg/L | 3.9/0.96 | 2.55/1.56 | 2.64/0.69 | 2.42/0.44 | 2.15/0.49 | 3.39/0.64 | 3.56/0.81 | 2.95/0.36 | 3.31/0.24 |
| Estimated $AUC_{0-12\ hr}$, mg·h/L | 25.0 | 24.4 | 20.9 | 18.0 | 16.4 | 25.7 | 25.6 | 19.8 | 21.3 |
| Estimated plasma GCV half-life, hr | 11.4 | 29† | 11.4 | 6.7 | 5 | 4.2 | 4.7 | 2.9 | 2.4 |
| Blood CMV viral load (log), copies/mL | 6607 (3.82) | 562 (2.75) | 0 | 0 | - | 0 | - | - | 0 |
| Creatinine, mg/dL | 0.76 | 0.68 | 0.53 | 0.55 | - | 0.48 | - | 0.4 | - |
| Platelet count, $\times 10^9$/L | 93 | 88 | 57 | 130 | 133 | 219 | - | - | 227 |
| Neutrophils, $\times 10^9$/L | 2.8 | 3.8 | 6.2 | 3.1 | 2 | 6.7 | - | - | 4.4 |

*AUC, area under the curve; CMV, cytomegalovirus; DOL, day of life; GCV, ganciclovir; IV, intravenous; V-GCV, valganciclovir*

* For each infant, relevant clinical parameters used for dose adjustment are presented. The viral loads and hematologic values reported are the closest to the ganciclovir plasmatic measurement and may not have been measured on the same day.

† This calculated half-life was considered as an outlier and thus was not considered for dose adjustment and excluded from the Figure.

to 20 mcg/mL). At DOL 21, the patient's viral load significantly decreased but his condition remained precarious with profound thrombocytopenia and important abdominal distension. On DOL 27, he underwent surgical treatment with resection of 9 cm of necrotic ileum. A quantitative PCR test performed on the resected intestinal segment showed positivity for CMV with 42,658 copies/mL and 4.63 $\log_{10}$ copies/mL, but CMV antibody immunohistochemistry was negative. No intranuclear or intracytoplasmic inclusions were found on routine histology. Blood CMV PCR testing became negative on DOL 28 and the patient's condition slowly improved. Treatment was switched to oral valganciclovir at 16 mg twice a day (7.4 mg/kg/dose) given simultaneously with enteral feeding on DOL 59, but IV ganciclovir treatment was reinstated at DOL 63 and 116 prior to surgical lysis of adhesions and closure of his ileostomy. Oral valganciclovir was reinstated on DOL 66 and 161 when enteral feeding was tolerated. At discharge, valganciclovir was increased to the term infant dose of 16 mg/kg/dose every 12 hours and was stopped after a 6-month treatment course. Hearing screening test performed at 34 weeks of postmenstrual age was normal.

At 18 months of corrected age, Bayley-III scores were 80, 74, and 79 on cognitive, language, and motor aspects, respectively, for both twins (Bayley-III scores of <85 indicating developmental delay). Auditory evoked potentials were satisfactory, as well as fundoscopic examination in both infants' follow-up.

Several ethical issues were considered. The mother was informed of the challenges of the treatment adjustment in regard to the prematurity and the use of TDM. The smallest possible blood volume was drawn for each analysis, and TDM was estimated from only 2 points to reduce blood samplings. Nearly all blood samples were coordinated with other samples required for the infants' clinical management. Finally, the mother gave her informed consent regarding this publication.

## Analytics Methods and Therapeutic Drug Monitoring

For the first TDM, blood samples were collected in EDTA microcontainers (0.25 mL) right before the dose, right after completion of the 60-minute IV ganciclovir infusion, and 3 hours after enteral valganciclovir treatment. Samples were processed into plasma (via centrifugation; 2500 g for 10 minutes) immediately, and then stored (−80°C), as used in previous work on ganciclovir and valganciclovir.[11] Plasma concentrations of ganciclovir were determined within 72 hours of sampling, using a high-performance liquid chromatography (HPLC) system. An internally (according to 2018 FDA guidance) and externally (KKGT antiviral drugs proficiency scheme) validated chromatographic method was used to determine ganciclovir in plasma samples. In brief, 100 µL of precipitating solution was added to 100 µL of samples from patients, calibration curve, and quality control. After vortex mixing and centrifugation, supernatants were transferred to auto-sampler vials and a volume of 70 µL was used for analysis. Chromatography was performed by using the 1260 Infinity HPLC system coupled to a diode array detector set at 254 nm (Agilent Technologies Canada Inc, St-Laurent, Canada). Chromatographic separation was carried out on a Phenomenex (Torrance, California, United-States) Synergy Hydro RP column (150 × 4.6 mm; 4 µm) using a mobile phase with a binary gradient. OpenLab CDS ChemStation Edition version C.01.04 [40] (Agilent Technologies Canada Inc, St-Laurent, Québec, Canada) was used to control the HPLC system and to process data (area integration, calculation, and plotting of chromatogram). The calibration curve ranging from 0.038 to 10 mcg/mL was quadratic with a correlation coefficient >0.999. The mean ± standard deviation absolute recovery of ganciclovir was 95.5% ± 2.5%. The method was precise with a mean intraday and interday coefficient of variation (for low, medium and high values) within 0.71% to 4.49% and 4.0% to 5.81 %, respectively. CMV viral load is assessed with a user-developed quantitative PCR assay using a standard curve based on quantified commercial controls (strain AD169, Advanced Biotechnology, Columbia, Maryland, United-States).

The timing of sampling was determined by the pharmacy and medical teams. All blood samples were collected at steady state, usually 3 to 4 days after dose adjustment. For example, the first TDM for the first twin was performed on the fourth dose, while ganciclovir was administered every 24 hours. The targeted AUC over 12 hours ($AUC_{0-12\ hr}$) was 27 mg·h/L.[3] For the very first TDM performed for each infant, 3 samples were taken initially: immediately before the infusion, at the end of the 1-hour infusion, and 10 hours after the beginning of the infusion. Because the first TDM confirmed the first-order elimination of ganciclovir and considering the importance of protecting the blood capital of preterm infants, subsequent TDM included only 2 samples, a trough and a peak concentration. Considering the prolonged plasma half-life of ganciclovir in the neonatal population, the estimated AUCs were calculated with the trapezoidal method with only these 2 measures (see Supplemental Figure), assuming that the overestimation of the AUC would be minimal. Moreover, assuming that trough concentrations do not vary significantly between contiguous doses at steady state, we used the measured pre-dose trough value and transposed it to estimate the 12 hours post-dose value of the second trapeze.

## Discussion

**Clinical Manifestations and Diagnosis of Congenital Cytomegalovirus Infection in Preterm Neonates**. Symptomatic cCMV infection may present as jaundice, intrauterine growth restriction, thrombocytopenia, chorioretinitis, hepatosplenomegaly, NEC, skin manifestations such as petechiae or purpura, and neurological manifestations such as microcephaly, ventriculomegaly, and periventricular calcifications.[3] While the prevalence of cCMV in preterm infants is similar to that of term infants, the former are at increased risk of severe manifestations.[6,12,13] Cases of disseminated cCMV infection presenting as severe sepsis with multiorgan involvement in preterm infants have been described, as well as CMV colitis mimicking NEC.[14,15]

A cCMV infection can also lead to long-term consequences, with about 10% to 15% of asymptomatic neonates developing hearing loss or another permanent neurologic sequela. In symptomatic neonates, this proportion reaches 30% to 65%.[4,16] While CMV and prematurity can independently influence the long-term prognosis and neurodevelopmental outcomes of children, few data exist on the burden of the 2 conditions occuring simultaneously. A study conducted by Turner et al[6] described higher rates of disability in CMV-positive VLBW neonates than in their infected-term or non-infected VLBW counterparts, with high rates of hearing loss (67%), abnormal neuroimaging (72%), and adverse developmental motor outcomes (43%).[6] These results are suggestive of the important burden of cCMV in preterm infants and highlight the importance of having better data on the use and effect of antiviral treatment in this population.

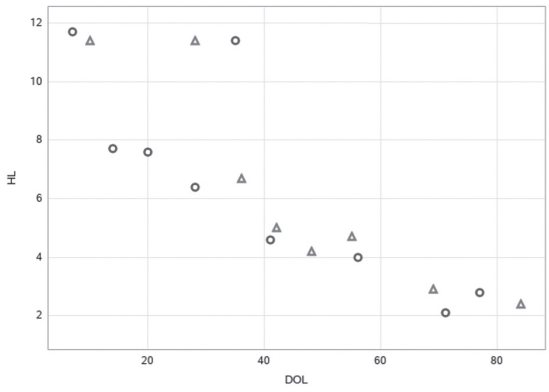
Diagnosis of cCMV infection is usually confirmed with the demonstration of the virus or viral antigens in the saliva, urine, or blood in the first 3 weeks of life.[1,17–19] While viral culture is considered the traditional gold standard technique for virus detection, PCR amplification of viral DNA is increasingly used as routine testing for CMV, given its high sensitivity,[1,18] and may also have prognostic value.[20] Our patients' presentation was in keeping with symptomatic congenital CMV, given the detection of CMV within 3 weeks of birth, in association with thrombocytopenia. The second twin also presented with a relative intrauterine growth retardation and developed severe NEC. Cytomegalovirus viral load was concomitantly increasing, which was suggestive of possible gastrointestinal involvement secondary to the progression of infection. However, while PCR testing performed on the resected intestine was positive for CMV, the histopathologic evaluation did not reveal the hallmarks of CMV colitis, such as inclusion bodies. This situation highlights the challenging aspect of differentiating between CMV-associated colitis and NEC in preterm infants. In addition to the complete targeted workup, including laboratory testing for renal and liver functions, complete blood count, brain imaging, as well as audiology and ophthalmology evaluations, some experts also recommend lumbar puncture as part of the evaluation of cCMV because detection of the virus in CSF is associated with symptomatic infection and SNHL at birth.[21] In our cases, the second twin, for whom CMV was detected in the CSF, presented with more severe disease.

**Challenges of Congenital CMV Treatment in Preterm Infants**. Although finding an appropriate dosing regimen for ganciclovir in extremely preterm infants may be challenging, considering extensive fluctuation of pharmacokinetic parameters in the first weeks of life. However, treatment for cCMV still ought be initiated promptly because evidence supporting efficacy of antiviral treatment is limited to studies in which therapy is initiated within the first month of life.[22] However, there is no validated dosing regimen for ganciclovir and valganciclovir in extremely preterm infants. We aimed to overcome these challenges by using TDM for dose adjustments because it has been shown useful for treatment individualization in the neonatal population.[23]

***Therapeutic Drug Monitoring of Intravenous Ganciclovir***. In 2003, Kimberlin et al[4] demonstrated that treatment with IV ganciclovir given at 6 mg/kg every 12 hours decreases neurosensory complications associated with symptomatic cCMV in children born at 32 weeks of gestation and older. A previous study reported that IV ganciclovir doses of 4 and 6 mg/kg in children born after 32 weeks of gestation and with a birth weight ≥1200 g were associated with mean $AUC_{0–12}$ hr of 27 to 32 mg·h/L.[24,25] The target of 27 mg·h/L was used thereafter as an exposure target in all latter dose-finding studies with an acceptable range initially between 20 and 55 mg·h/L, and then tightened to between 23 and 36 mg·h/L.[7,25] However, no studies have confirmed the clinical validity of this target in VLBW or extremely low birth weight (ELBW) infants. Our literature review did not provide any useful data to guide appropriate dosing strategies for both ganciclovir and valganciclovir to achieve these targets in very premature infants. Only 2 case reports describing the use of TDM for ganciclovir and/or valganciclovir in ELBW have been published to date.[9,10] A report of 26 newborns, including preterm infants, showed considerable variability in reaching AUC target with standard dosing regimens and emphasizes the need to individualize doses in this population.[26] A clinical trial aiming to characterize the pharmacokinetics of ganciclovir in children born very prematurely has been recently conducted, but no infants born at <28 weeks of gestation and younger than 30 days of chronological age were enrolled.[27] (ClinicalTrials.gov Identifier: NCT01602614).

***Pharmacokinetic Considerations for Intravenous Ganciclovir in Neonates***. The pharmacokinetics of ganciclovir in neonates born at 32 weeks of gestation or more and ≥1200 g have been characterized in several studies, with pharmacokinetic parameters generally

**Figure.** Evolution of ganciclovir plasma half-life over time in both infants.




*DOL, day of life; HL, half life*

○ **Infant 1;** △ **Infant 2**

similar to adult values.[7,24,25,28,29] Over 90% of ganciclovir is eliminated by glomerular filtration and active tubular secretion. In newborns, renal function depends on gestational and postnatal age, associated comorbidities, and other pharmacologic treatments.[30]

Initially, plasma half-life of ganciclovir was prolonged in the presented cases: approximately 12 hours, compared with the reported adult half-life of 2.5 hours. This decrease in clearance can be attributed to immaturity of the renal function in extremely preterm infants, and to the superimposed renal insult associated with TTTS. As renal function matured, a noticeable decrease in plasma half-life was observed and reached term infant values at 10 weeks of postnatal age (37 weeks of postmenstrual age) (Figure). Over the 11 weeks of hospitalization, a significant variation in ganciclovir clearance was observed, consistent with the expected maturation changes during this period, as well as previous observations in older infants.[7] This evolution of renal function prompted adjustment of the IV ganciclovir and oral valganciclovir dose and administration interval (Table 2).

The infants were monochorionic diamniotic twins. The similarities in the evolution of their pharmacokinetic parameters after 6 weeks of chronological age might be related to their shared genome. However, disparities can be noted in their pharmacokinetic parameters in the first weeks of life, which could be attributed to the difference in their TTTS status and clinical presentation as the second twin's illness was more severe.

We did not attempt to assess the correlation between $C_{min}$ and AUC because we had non-independent data from only 2 children. This correlation could be relevant to evaluate in pharmacokinetic studies to reduce the burden of blood samples.

***Considerations for the Optimal Dosing of Oral Valganciclovir***. Valganciclovir is the L-valine ester of ganciclovir and is actively absorbed by intestinal peptide transporters, conferring a higher oral bioavailability than oral ganciclovir.[25,31] Valganciclovir has no antiviral activity itself but is rapidly converted into ganciclovir by intestinal and hepatic intracellular esterases. The oral bioavailability of various formulations of oral suspensions of valganciclovir has been studied, including the later marketed formulation, and reaches between 41% and 53% in neonates.[7,25,32,33] Oral administration of valganciclovir in ELBW infants raises the additional question of the ontogenesis of the intestinal peptide transporters involved in enteral absorption, as well as the activity of intracellular esterases involved in the hydrolysis of valganciclovir to ganciclovir.[31] As the infant ages, it would be expected that maturation of the enteral absorption during the first weeks of life would lead to fluctuation in drug exposure. However, studies have shown that as oral bioavailability increases, the previously mentioned maturation of renal clearance increases in parallel, and the estimated drug exposure (AUC) remains relatively stable.[7,25,31]

Previous pharmacokinetic studies have demonstrated that a valganciclovir dose of 16 mg/kg given orally every 12 hours leads to a similar drug exposure ($AUC_{0–12\ hr}$) as 6 mg/kg of IV ganciclovir given at the same interval.[7,25,31] The clinical efficacy of this regimen has been validated in randomized controlled trials.[8,31]

In our cases, upon switching to enteral treatment, the 6:16 ratio of ganciclovir to valganciclovir was used for dose conversion. Table 2 provides the estimated $AUC_{0–12\ hr}$ for IV and oral treatment in our patients. With this equivalence, the AUCs were within the target range upon switching from the IV to the oral route.

***Toxicities Associated With Ganciclovir and Valganciclovir***. *In vitro* studies have shown that ganciclovir inhibits viral replication at concentrations ranging from 0.02 to 5.75 mg/L ($IC_{50}$).[31,34] Mammalian cell proliferation is inhibited by ganciclovir at higher concentrations, for example, at >10 to 250 mg/L. However, hematopoietic stem cells can be affected at concentrations as low as 0.69 to 3.06 mg/L.[31] Therefore, a significant proportion of children treated with ganciclovir develop hematologic toxicity.

In a phase II study using ganciclovir in neonates, 34% of children developed neutropenia. However, no clear dose-toxicity relationship was observed.[29] Neutropenia has also been frequently reported, with grade 3 or 4 neutropenia in 63% of children treated with IV ganciclovir, leading to discontinuation of treatment in 8% of children.[4] In a subsequent study evaluating ganciclovir and valganciclovir, 38% of children developed grade 3 or 4 neutropenia.[7] In the latter study, doses were adjusted by TDM to target $AUC_{0–12\ hr}$ between 23 and 36 mg·h/L, which may explain the reduced occurrence of neutropenia. Thrombocytopenia (38%) and anemia (13%) were also reported in children treated with ganciclovir for cCMV.[7,29] The study by Kimberlin et al[7] found a correlation between maximal concentration ($C_{max}$) and

AUC and the occurrence of leukopenia and neutropenia, while the results from the study by Whitley et al[29] are more equivocal. Cytomegalovirus itself can cause neutropenia and thrombocytopenia, making it often difficult to disentangle the contribution of the infection from the toxicity of the antiviral. Other toxicities, such as renal or hepatic, have rarely occurred in these cohorts and long-term toxicities including gonadotoxicity have not been clearly linked to exposure.

**Therapeutic Drug Monitoring in Extremely Preterm Neonates: Recommendations**. The data derived from the serial AUCs bring valuable information on the evolution of enteral absorption and excretion of ganciclovir and valganciclovir in VLBW and ELBW infants with maturing pharmacokinetic parameters. However, TDM can be highly time-consuming and is associated with significant costs. Furthermore, to allow a precise estimation of drug exposure, serial measurements are required. However, to limit blood withdrawal in extreme preterm newborns with a limited blood capital, and following neurodevelopmental care recommendations in this vulnerable population, only 2 measurements were deemed necessary. Hence, the calculated AUCs in our 2 patients are mere estimates from limited samples and thus should be interpreted with caution. An alternative approach to TDM would have been to give the usual neonatal dosing regimen and to follow viral loads for efficacy and complete blood count for toxicity. However, this approach may be associated with a higher risk of hematologic toxicity, leading to treatment interruption and thus possibly inducing drug resistance. In our opinion, the interindividual and intraindividual variability in the pharmacokinetics of ganciclovir and valganciclovir in VLBW or ELBW infants, combined with the variability in renal function maturation, justify the use of TDM in this setting. The current available literature on cCMV suggests to aim for an $AUC_{0–12\,hr}$ of 27 mg·h/L considering efficacy standpoint; however, no toxicity threshold has been clearly established. An initial IV ganciclovir dosing of 2 mg/kg every 12 hours for infants <28 weeks of postmenstrual age and 4 mg/kg every 12 hours for infants between 28 and <32 weeks of postmenstrual age has been suggested in our institution and should provide an $AUC_{0–12\,hr}$ in the targeted range for infants with normal renal function. The 2 children in the case presented herein had some initial renal impairment associated with their TTTS status, which prompted us to be more conservative with the starting dosage. Further data from clinical and pharmacokinetic trials on the use of ganciclovir in preterm neonates are required to validate this regimen. Given that clinical studies have included preterm infants from 32 weeks' gestation, the usual neonatal doses of ganciclovir (6 mg/kg IV every 12 hours) and valganciclovir (16 mg/kg orally every 12 hours), without TDM but with tight safety monitoring, are recommended as the infant approaches 32 weeks of postmenstrual age.

## Conclusion

Preterm neonates should be carefully assessed for possible clinical manifestations of cCMV and appropriate diagnostic tools should be ordered when suspected. The paucity of data, combined with the difficulty to attain targeted AUC for ganciclovir treatment in the neonatal population, confirms the relevance of TDM use in this setting. An adjustment of ganciclovir dosing in preterm neonates with cCMV should be considered, but further data are needed to validate a specific regimen in this population. The presented cases provide important insights on the evolution of ganciclovir clearance in preterm infants with maturing pharmacokinetic parameters.

## Article Information

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