Anti-viral therapy for congenital cytomegalovirus infection: pharmacokinetics, efficacy and side effects.

Arianna Mareri, Stefania Lasorella, Giulia Iapadre, Maria Maresca, Renato Tambucci, and Giovanni Nigro

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Resumen.

La infección congénita por citomegalovirus (CMV) es la infección congénita más común en el mundo, con aproximadamente 0,5-2% de todos los recién nacidos vivos, y puede causar daño neurológico y neurisensorial severo temprano o tardío. Aunque ningún fármaco ha sido autorizado para el tratamiento de la infección congénita por CMV, ganciclovir (GCV) por vía oral y su profármaco, valganciclovir (val-GCV), están siendo cada vez administrados a lactantes sintomáticos, para mejorar resultados de desarrollo neurológico y auditivo. Otros potencialmente eficaces para el tratamiento de la enfermedad por CMV congénita son Foscarnet (FOS) y Cidofovir (CDV), que sólo se han administrado en algunos casos. Se hizo una búsqueda bibliográfica para publicaciones basada en la evidencia o artículos científicos que evaluaron la farmacocinética, eficacia y efectos secundarios de GCV / val-GCV y otros medicamentos anti-virales.

Observaciones finales

La infección congénita por CMV es muy común en todo el mundo, ya que el CMV es altamente placentotropico y la transmisión materno-fetal puede generar tanto la infección materna primaria como recurrente. Está aumentando la necesidad de terapias anti-virales en lactantes y neonatos, debido a las consecuencias de secuelas graves inmediatas o tardías, las mayorías neurológicas o auditivas. Ninguno de los cuatro antivirales actualmente disponibles, GCV, valGCV, FOS, y CDV, han aprobado indicaciones para su uso en niños. A pesar que hay datos limitados en cuanto a la dosis, PK, seguridad y eventos adversos para los FOS y CDV, GCV, y su profármaco oral de val-GCV, han sido los fármacos antivirales más estudiados en la población infantil y recién nacidos. El volumen de distribución, el clearence y la vida media de GCV, cuando se ajusta para el peso, son similares a los de los adultos. La neutropenia es el efecto secundario más frecuente asociado con GCV y val-GCV, mientras que la toxicidad renal significativa puede ocurrir durante la terapia CDV. La administración de FOS también puede dar toxicidad renal, así como los desequilibrios de electrolitos significativos. Toxicidades potenciales de GCV, val-GCV, y CDV, observados en estudios en animales, incluyen la carcinogénesis, teratogénesis y azoospermia reversible. Sin embargo, val-GCV parece ser la droga más fiable anti-CMV, dados los resultados favorables que se pueden obtener mediante la administración prolongada y la baja tasa de efectos secundarios en los recién nacidos inmunocompetentes a término.

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ORIGINAL ARTICLE

Anti-viral therapy for congenital cytomegalovirus infection: pharmacokinetics, efficacy and side effects

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Abstract

Congenital cytomegalovirus (CMV) infection is the most common congenital infection in the world with approximately 0.5–2% of all live born infants, and can cause early or late severe neurological and neurisensorial damage. Although no drug has been licensed for therapy of congenital CMV infection, ganciclovir (GCV) and its oral pro-drug, valganciclovir (val-GCV), is increasingly being administrated to symptomatic infants, to improve neurodevelopmental and auditory outcome. Other potentially efficacious for therapy of congenital CMV disease are foscarnet and cidofovir, which have only been administered in few cases. A literature search was performed to look for evidence based or scientific articles evaluating pharmacokinetics, efficacy, and side effects of GCV/val-GCVand the other two anti-viral drugs.

Keywords

Anti-viral therapy, cidofovir, congenital cytomegalovirus infection, foscarnet, ganciclovir, valganciclovir

History

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Introduction

Congenital cytomegalovirus (CMV) infection is the most common congenital infection, ranging from about 0.6% in developing countries. In fact, it follows both primary and recurrent infection in pregnancy and can persists for years in the body fluids of infected people, mostly children [1]. Fetal transmission occurs in 30–70% of women acquiring primary infection or in 0.5–2% of women with preconceptional immunity. Approximately 10% of all infected neonates are symptomatic and 10% will develop sequelae later in life, especially neurodevelopmental damage. However, the rate of symptomatic infants who were infected in the first half of pregnancy can be upto 50% [1,2]. The most serious consequences of congenital CMV infection occur in 30–50% of the symptomatic infants, and include microcephaly, periventricular calcifications, cerebral and cerebellar dysplasia, hyper- or hypotonia, sensorineural hearing loss (SNHL) and seizures [2]. A wide range of neurological manifestations are due to an indirect effect of intrauterine infection, which impaired the placental capacity to provide oxygen and nutrients to the developing fetus; whereas others such as SNHL are more likely due to direct viral damage to the fetal cochlear cells [3]. The evidence for this is that hearing at birth may be normal but can slowly progress over the initial years of age, as reported in a study by Fowler et al., where the late-onset hearing loss at 6 years is 18% [4]. The social costs for surviving children with congenital CMV infections are approximately $1.9 billion/year [5]. There are currently three anti-viral drugs which could be used for the treatment of congenital CMV infection: ganciclovir (GCV)/valganciclovir (val-GCV), foscarnet (FOS) and cidofovir (CDV). The most common drugs used are GCV and its mono-valyl ester pro-drug, which are structurally similar to acyclovir but with a greater inhibitory activity against CMV. We performed a systematic review concerning postnatal anti-viral therapy for congenital CMV infection, using electronic databases for search of relevant studies. Only randomized controlled trials (RCT), observational studies or case series were included [6].

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Ganciclovir

Pharmacology and pharmacokinetic

Ganciclovir or 9-[(1,3,-dihydroxy-2-propoxy)methyl] guanine (DHPG), is an acyclic analog of the nucleoside guanosine capable of inhibiting all herpes viruses, mostly CMV, with a chemical structure similar to that of acyclovir (ACV), which is active *in vivo* only against herpes simplex and varicella zoster viruses. To achieve anti-viral activity, GCV requires intracellular phosphorylation, which starts with conversion to ganciclovir 5′-monophosphate by a viral kinase, phosphotransferase, encoded by the CMV gene UL97 [7]. Subsequently, cellular kinases catalyze the development of GCV diphosphate and GCV triphosphate, which is present in 10-fold greater concentrations in CMV-infected cells than uninfected cells. After the release of pyrophosphate, GCV monophosphate is incorporated into the end of a growing chain of viral DNA, slowing replication. In addition, GCV triphosphate serves as a poor substrate for chain elongation, thereby disrupting viral DNA synthesis by a second route [8].

GCV is poorly absorbed after oral administration, with a bioavailability of approximately 5%. After oral administration of standard adult doses, maximum serum GCV concentrations typically are 0.5–1.5 μg/mL. After IV administration, maximum serum GCV concentrations of 7–19 μg/mL are achieved. *In vitro*, the median concentration of GCV that inhibits CMV replication ranges from 0.1 to 3.48 μg/mL [8]. Oral bioavailability is significantly improved with val-GCV, the L-valyl ester of GCV, with an average value of 59.4 ± 6.1% reported from premarketing clinical trials in adults. After oral administration, val-GCV is rapidly cleaved by esterases in the intestine wall and liver to form active GCV.

The pharmacokinetic (PK) profile of GCV and val-GCV in infants and children has been evaluated in several studies presented in Table 1. In 1993, Trang et al. evaluated the PK characteristics of IV GCV in 27 neonates with congenital CMV infection, who were randomized to GCV therapy at either 4 or 6 mg/kg per dose every 12 h for 6 weeks [9]. The maximum serum concentration was 5.5 ± 1.6 mcg/mL after a dose of 4 mg/kg and 7.0 ± 1.6 μg/mL after 6 mg/kg. The mean elimination half-life was 2.4 h. In 1996, Zhou et al. re-analyzed the same 27 infants by non-linear mixed-effects modeling analysis, trying to identify individual characteristics of infants that may account for variations in drug PK [10]. The authors found that the GCV clearance and serum creatinine increase linearly and the volume of distribution is linear function of the weight of the infant. In 2003, a study by Zhang et al. involving 11 children (mean age 11.0 ± 3.9 years) showed the maximum concentration after an IV GCV dose of 5 mg/kg bis-in-die (bid) for 15 d was 11.77 ± 2.82 μg/mL [11]. Administration of an oral dose of 50 mg/kg bid for 3 months produced a maximum concentration of 2.70 ± 1.07 μg/mL. The authors concluded that dosage regimen of 5 mg/kg per 12 h of IV GCV followed by 50 mg/kg bid of oral GCV produced adequate serum GCV concentrations for treatment. Burri et al. analyzed the PK of val-GCV in a 6-year-old girl with congenital HIV-CMV confection [12]. Single dose PK of IV GCV 4.4 mg/kg and oral val-GCV 13.2 and 26.3 mg/kg were studied with high performance liquid chromatography/tandem mass spectrometry. Oral val-GCV achieved therapeutic and dosage-proportional plasma concentrations in the child. In 2007, Galli et al. studied eight infants aged 4–90 d with symptomatic congenital CMV infection, who were given val-GCV after a first week of IV GCV treatment (5 mg/kg/bid) [13]. The first four infants received val-GCV at the dose of 15 mg/kg/die and the next four infants had val-GCV 15 mg/kg/bid. Only the infants treated with val-GCV 15 mg/kg/bid showed drug concentrations that were statistically not different from IV GCV: a peak concentration of 1.95 μg/mL was observed in the IV GCV group and 3.1 μg/mL in the val-GCV 15 mg/kg/bid group. Studies performed by Acosta et al. and Kimberlin et al. in 24 neonates with symptomatic congenital CMV disease showed that a dose of 16 mg/kg/bid of val-GCV provides GCV exposure comparable to that of a 6-mg/kg dose of IV GCV [14,15]. However, Meine Jansen et al. reported a continuous adaptation of val-GCV doses from 280 to 850 mg/m^2 to achieve target levels of GCV that made CMV DNA undetectable in the urine, concluding that it is not possible to use a fixed-dosing regimen for val-GCV in infants [16]. The manufacturer recommends that doses should be calculated based on body surface area and creatinine clearance. In patients receiving IV GCV who have mild renal dysfunction, the dose should be reduced by 50% to a daily dose of 2.5 mg/kg. The current recommended treatment regimen, which is published in the British National Formulary of Children (BNFC www.bnfc.org), is: GCV 6 mg/kg/dose IV bid for 6 weeks or val-GCV 15–18 mg/kg given orally bid.

Clinical effects in immunocompetent patients

Numerous studies and case reports concerning the virological and clinical effects of GCV have been published (Table 2). Except from a few infants with severe pneumopathy or hepatopathy, all treated infants had at least one severe neurological manifestation (microcephaly, seizure, hyper or hypotonia) and/or imaging abnormality such as periventricular calcifications, cortical or cerebellar atrophy, cystic leukomalacia, cerebral dysplasias mostly including polymicrogiria and lyssencephaly, and hearing loss or chorioretinitis. In 1994, a pilot study compared two regimens of GCV treatment started within the first 2 weeks of life in two groups of six neonates with congenital CMV infection [17]. Six newborns in group 1 were only treated with GCV 5 mg/kg bid for 2 weeks. Six children in group 2 were treated with GCV 7.5 mg/kg bid for 2 weeks, followed by 10 mg/kg three times a week for 3 months. In group 1, viral shedding disappeared in 3/6 infants, where in group 2 all six infants showed cessation of viruria. Neurological development at the age of 18 months was normal in two children of group 1, but in four of group 2.

Table 1. Pharmacokinetic data for ganciclovir, valganciclovir, and cidofovir administered to neonates in published studies.

References	Drug	Dose range (mg/kg/d)	Vd (mL/kg)	Cmax (mcg/mL)	Tmax (hour)	CL (mL/h/kg)	Minimum viruria copies/mL
Trang et al. [9]	GCV iv	4	669 ± 70	5.5 ± 1.6	1	2.4	ND
	GCV iv	6	749 ± 59	7.0 ± 1.6	1	2.4	ND
Burri et al. [12]	GCV iv	4.4	ND	4.591	1	ND	ND
	valGCV	13.2	ND	0.109	1,5	ND	ND
	valGCV	26.3	ND	0.267	1,5	ND	ND
Galli et al. [13]	GCV iv	10	ND	1.95	1	ND	ND
	valGCV	15	ND	0.42	1,5	ND	3.72 ± 0.71
	valGCV	30	ND	3.1	1,5	ND	2.66 ± 0.51
Zhang et al. [11]	GCV iv	5	ND	11.77 ± 2.82	1	ND	0 (after 16 ± 11 d)
	GCV oral	50	ND	2.70 ± 1.07	1	ND	
Breddemann et al. [43]	CDV	2.5	560	4.62	ND	257	ND

Cmax, maximum plasma concentration; CL, clearance; Vd, volume of distribution; Tmax, time to reach Cmax; iv, intravenous; ND, not available data.

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Table 2. Clinical response after treatment with ganciclovir, valganciclovir, and foscarnetin immunocompetent infants with congenital cytomegalovirus infection.

References	No. patients	No. group patients	Drug	Dose mg/kg/d	Weeks therapy	F-U mo	Favorable outcome			
							Cerebropathy	Hearingloss	Chorio-retinitis	Other
Nigro et al. [17]	12	6	GCV iv	10	2	3–6	2/6	ND	0/2	ND
		6	GCV iv	$15 + 10 \times 3$ times/week	2 + 12		5/6		2/2	
Whitley et al. [18]	42	14	GCV iv	8	6	36	8/33	3/17	8/14	ND
		28	GCV iv	12	6					
Michaels et al. [21]	9	9	GCV iv	10 + 5	2–4 + 22–72	12–48	3/9	3/9	ND	ND
Kimberlin et al. [19]	100	25	GCV iv	12	6	6	ND	21/25	ND	ND
Nigro et al. [28]	3	3	GCV iv + oral	10 + 70	3 + 8	56–72	ND	ND	ND	Enterocolitis 3/3
Del Rosal et al. [24]	13	4	GCV iv + valGCV	12 + 32	3–6 + 12–36	12	0/2	7/11	ND	ND
		9	valGCV	32	12–36					
Kimberlin et al. [25]	96	47	valGCV	32	6	24	6-month group: better Bayley III scores	22/31	ND	ND
		49	valGCV	32	24	24		32/37		
Nigro et al. [39]	1	1	FOS	180 + 100 3/week	3 + 12	ND	1/1	ND	ND	Liver fibrosis, pneumonia
Knorr et al. [40]	1	1	FOS	100	3	ND	ND	ND	ND	HLH

iv, intravenous; GCV, ganciclovir; FOS, foscarnet; ND, not available data; HLH, hemophagocytic lymphohistiocytosis.

Three infants with bilateral hearing loss (two in group 1 and one in group 2) did not improve, while two infants with initial chorioretinitis had normal visual examination at 18 months. Early multicenter studies conducted by the National Institute of Allergy and Infectious Diseases Collaborative Anti-viral Study Group (CASG) focused on the potential long-term benefits of anti-viral therapy. Phase I PK and pharmacodynamic studies indicated that GCV therapy of congenital CMV infection was associated with decreased virus load and improved laboratory abnormalities [9,10]. A subsequent phase II study CASG compared two 6-week-regimen therapy courses in neonates with congenital CMV and neurological diseases (8 mg/kg/d versus 12 mg/kg/d), in 14 and 28 babies, respectively [18]. The infants treated with the higher GCV dosage showed a more pronounced anti-viral effect that was associated with an improved neurological examination at 18 months of age. Hearing data were available for 30 of 42 children and did not differ by treatment group. Of the 13 babies with normal baseline hearing, 11 became abnormal despite treatment. Of the 17 babies with abnormal baseline hearing, three had normal hearing on follow-up. Of 14 infants with retinitis (two in the 8 mg/kg group, 12 in the 12 mg/kg group) eight had normal visual function at 6 months. Of the infants with normal ophthalmologic evaluation at baseline, three developed retinal CMV scarring. Eight (24%) of 33 children evaluated at 2 years met all developmental milestones and showed no neurologic impairment. Neurologic status did not differ by medication dose. In 2003, Kimberlin et al. and CASG published a phase III randomized trial including 100 infants $\leq$1 month of age, $\geq$32 weeks' gestation and weighing $\geq$ 1200 g at birth, having evidence of cerebral disease, who were randomly assigned to receive GCV treatment (6 mg/kg every 12 hours for 6 weeks) or no treatment [19]. The primary endpoint was improved brainstem-evoked response (BSER) between baseline and 6 month follow-up (or no deterioration at the 6 month follow-up if the baseline BSER was normal). Among totally evaluable ears, 69% of the 25 patients who received GCV met the primary endpoint as opposed to 39% of the control group. No patients receiving GCV had worsening of their hearing between baseline and 6 months versus 7 of 17 (41%) control patients ($p < 0.01$). The authors concluded that GCV therapy having begun in the neonatal period in infants with neurological CMV infection prevents hearing deterioration at 6 months and may prevent hearing deterioration at $\geq$1 year. A subsequent randomized controlled trial by the same research group suggested that GCV may also reduce neurodevelopmental delays [20]. Also in 2003, Michaels et al. described nine infants with congenital cerebral involvement by CMV, including microcephaly (five infants), intracranial calcifications (six), and hearing loss (five) [21]. IV GCV was started between 7 d and 11 months of age and administrated for a median of 12 months at the initial dosage of 10 mg/kg/d as a maintenance dosage of 5 mg/kg/d after 2– 4 weeks. After IV GCV for 5.5–18 months, oral GCV was administrated (550 mg/m^2/dose three times/d) for 6–36 months. All children were followed for a median of 2 years. No child had progression of hearing loss; monolateral improvement occurred in two. In 2005, Tanaka-Kitajima et al. reported on recovery or improvement of chorioretinitis,

thrombocytopenia and anemia in six infants with symptomatic congenital CMV infection treated with 5–12 mg/kg bid of GCV for a median of 14 weeks [22]. All patients developed neurologic deficits and hearing loss, which improved in two children at follow-up. In 2009, Lombardi et al. reported on improved hearing (from moderate to mild) in 2/8 infants aged ≤30 d with symptomatic congenital CMV infection, who received val-GCV (15 mg/kg bid) for 6 weeks [23]. The remaining four infants with normal hearing at baseline of a 12 case series showed normal hearing at 6 months. An improved hearing, from 85% decreased hearing at baseline to 50% at 12 months (by ears, from 18 to 9), was also reported by Del Rosal et al. in a retrospective case series of 13 infants with congenital CMV infection and CNS involvement, who were treated with val-GCV for a median duration of 6 months; 4 of them also received IV GCV (12 mg/kg/d bid) [24]. Recently, the results of a randomized, placebo-controlled trial of val-GCV therapy in 86 neonates with symptomatic congenital CMV disease, comparing 6 months versus 6 weeks of therapy, were reported by Kimberlin et al. [25]. A statistically significant improvement in hearing (in one or both ears) or a stable normal hearing were shown by the 6-month group compared to the 6-week group at 12 months (73% versus 57%, $p = 0.01$) and at 24 months (77% versus 64%, $p = 0.04$). At 24 months, the 6-month group, as compared with the 6-week group, had also better neurodevelopmental BayleyIII scores on the language-composite component ($p = 0.004$) and receptive-communication scale ($p = 0.003$).

Apart from neurological manifestations, hearing loss or chorioretinitis, few studies described the use of GCV in children with congenital CMV infection and other associated diseases. Nigro et al. reported on 20 children with CMV-associated liver disease, of whom 6 were immunocompetent and 14 were immunocompromised (9 had AIDS and 5 had solid tumors) [26]. Like in a previous study, better results were obtained using a single GCV course at high dosage (7.5 mg/kg twice daily for 14 d) followed by prolonged therapy (10 mg/kg three times weekly for 3 months) than by several courses with low dosages (5 mg/kg twice daily for 8–86 d, mean 21). Fischler et al. reported on six newborns with CMV-associated intra or extra-hepatic neonatal cholestasis [27]. Four patients, including one with biliary atresia, responded biochemically and virologically to the treatment with GCV, whereas two children did not. In a patient, GCV was discontinued because of hypoglycemia. Nigro et al. reported on three infants with prenatal or immediately postnatal CMV infection associated with persistent enterocolitis requiring total parental or nasal gastric feeding [28]. All the patients, treated with 1–2 month courses of oral GCV at the dosage of 70 mg/kg, recovered and re-introduced oral feed. After 17 month and subsequent follow-ups, all children showed negative CMV-DNA stools and a good clinical outcome. Preventive therapy of asymptomatic CMV infected newborns is controversial. The only available paper concerns 23 asymptomatic neonates, 12 of whom were treated with GCV (10 mg/kg) for 21 d, and 11 were observed without therapy [29]. A 4–10 years hearing function follow-up showed SNHL in two untreated children while all treated children had normal hearing function.

GCV/val-GCV resistance

The primary mechanism of viral resistance to GCV is through mutations in the UL97 kinase gene: GCV-resistance mutations at UL97 codons 460, 520 and 590–607 impair the phosphorylation of GCV that is necessary for its anti-viral activity, presumably by altering substrate recognition (Figure 1). The first study on GCV resistance was done in 1998 by Wolf et al., who examined six children with primary combined immunodeficiency and CMV infection, using sequence analysis of the CMV UL97 gene and viruses susceptibility assay [30]. Mutations were found in four of the six children. All mutations were detected within 10 d to 3 weeks from initiation of therapy. In the great majority of cases, GCV-resistance occurs in immunocompromised patients but in 2012 Campanini et al. reported a case of drug-resistance in a congenitally CMV infected and immunocompetent newborn, who had four known UL97 mutations (A594T/V, M460V/I, C592G), a new amino acid substitution (C607S) and a new deletion (597–600) in one of the three UL97 hot spots for GCV/val-GCV resistance [31]. Subsequently, Choi et al. described a case of an infant with congenital CMV disease treated with val-GCV, in whom GCV resistance was suspected because of a 50-fold increase in viral load after 6 weeks of oral therapy [32]. Another site for mutations that may confer viral resistance to GCV is the UL54 gene that encodes the viral DNA polymerase. Erice reported that UL54 mutations account for only 5% of GCV isolated resistance but, when they occur subsequently to UL97 mutation, can confer high level of GCV resistance and various degree of cross-resistance to the second-line drugs including FOS and CDV [33].

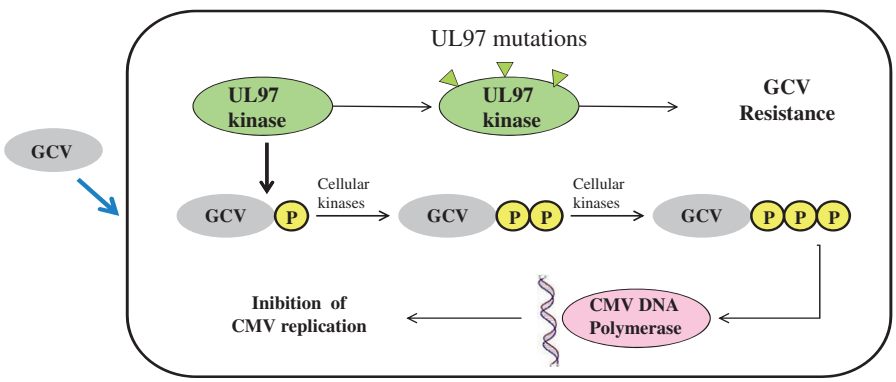

Figure 1. Cytomegalovirus mechanism of drug resistance. P = phosphotransferase.

Side effects

Myelosuppression, including granulocytopenia, anemia, thrombocytopenia, often is a dose limiting toxicity of VGC in immunocompromised patients and in preterm newborns [34]. Neutropenia is managed by dose reduction and/or addition of growth factors (i.e. granulocyte colony-stimulating factor orgranulocyte-macrophage colony-stimulating factor). However, the incidence of neutropenia in CMV-infected infants varies significantly. Nigro et al. found no side effects in the low-dose short-duration regimen and neutropenia only in one of high-dose long-duration regimen of GCV therapy [17]. Similar results were reported by Michaels with only one child over nine, who developed neutropenia with an absolute neutrophil count of $<500 \times 10^6$ cells/L [21]. On the contrary, in the 2003 study by Kimberlin et al., neutropenia occurred very frequently (63%) in GCV-treated infants, but a 21% rate was also evidenced in control patients [19]. In the case series reported by Del Rosal et al., 6/13 infants developed neutropenia, but none requiring granulocyte colony-stimulating factor [24]. In the recent paper by Kimberlin et al., grade 3 or 4 neutropenia occurred in 21% of the infants in the 6-month group during the last 4.5 months of the study but in 27% of those in the 6-week group ($p = 0.64$) [25]. The maintenance of a central line or continuous infusion peripheral line for the GCV administration was associated with complications (line replacement, thrombophlebitis, secondary infections) in a variable range from 10 to 66% of treated patients [18,21]. Other rare side effects are raised liver enzymes, hypokalemia and renal impairment. All these side effects are reversible after stopping therapy for 3–7 d or decreasing the dose of the drug according to company product information (http://www.rocheuk.com; accessed December 2010). Animal experiments showed that high-dose GCV induces reversible testicular damage with reduced sperm viability and may have carcinogenic effects, but long-term effects in humans are not yet established [7].

Foscarnet

Pharmacokinetics and adverse effects

Foscarnet (FOS), the the tri-sodium salt of phosphonoformic acid, a white, crystalline powder containing six equivalents of water of hydration with a molecular formula of $Na_3CO_5P{\cdot}6\ H_2O$ and a molecular weight of 300.1, is the only anti-herpes drug that is not a nucleoside analog. This drug inhibits the activity of the viral DNA polymerase by binding to the pyrophosphate binding site and blocking cleavage of pyrophosphate from the terminal nucleoside triphosphate added to the growing DNA chain. FOS does not require phosphorylation by kinases and is therefore active against pUL 97 kinase variations that confer resistance to GCV/val-GCV [34]. FOS is poorly absorbed after oral administration, with a bioavailability of only 20%. The PK data of FOS are limited regarding tissue distribution, but cerebrospinal fluid concentrations are about two thirds of those in serum. Eighty percent of administered dose of FOS is eliminated unchanged in the urine; the half-life is 48 h. Dose adjustments are necessary even in the presence of minimal degrees of renal dysfunction. The most common adverse effects of FOS are nephrotoxicity and metabolic derangements. Evidence of nephrotoxicity includes increased blood urea nitrogen, proteinuria, acute tubular necrosis, crystalluria and interstitial nephritis. Pre-existing renal disease, concurrent use of other nephrotoxic drugs, dehydration, rapid or continuous intravenous infusion of drug are risk factors for developing renal dysfunction. PK and safety of FOS in pediatric patients, including infants, has not been established [35]. The usual FOS dose in adults for CMV infection is 180 mg/kg/d in three divided doses for 14–21 d, followed by a daily maintenance dose of 90–120 mg/kg. FOS is considered a second-line therapy for the treatment of CMV retinitis in AIDS patients due to its relatively toxic safety profile and for acyclovir-resistant mucocutaneous HSV infection. Its use in systemic CMV infections has been limited to patients who are failing GCV therapy, presumably due to drug resistance, or those who cannot be treated with GCV due to dose-limiting [34].

Clinical effects

A multicenter, randomized clinical trial compared FOS with GCV in the treatment of CMV retinitis in 234 patients with AIDS, who were randomly given GCV (127 patients) or FOS (107 patients) [36]. Among the patients assigned to GCV 65 died, contrary to 36 of those assigned to FOS ($p = 0.007$; RR: 1.79). The median survival was 8.5 months in the GCV group and 12.6 months in the FOS group. There was no difference between the two treatment groups in the rate of progression of retinitis ($p = 0.751$; RR: 0.95). These results suggest that treatment with FOS allows for a longer survival than GCV therapy in patients with AIDS and CMV retinitis, although the patients may not tolerate FOS as well as GCV. However, FOS and GCV have been shown to inhibit synergistically CMV replication by *in vitro* studies and a case report of an HIV-infected infant with encephalitis and retinitis [37,38].

Only two cases of immunocompetent children with congenital CMV infection treated with FOS have been reported. In 2004, Nigro et al. described the case of a 41-week gestation boy, who had prenatally shown hepatomegaly and ascites associated with CMV DNA detection in the amniotic fluid [39]. At birth presented with jaundice, hepatomegaly, liver fibrosis, right microphthalmia, cataract, interstitial pneumonia and hyperechoic lesions in the basal ganglia. After biopsy, CMV DNA was detected in the liver. Since the parents refused GCV therapy because of possible side effects, FOS at 60 mg/kg was administered every 8 h for 3 weeks followed by 100 mg/kg three times a week for 3 months. Brain ultrasound and chest X-ray were normal within the first 3 months and the liver biopsy was negative for CMV DNA detection at 5 months. A 10-year follow-up showed normal liver function and neurological development. In 2006, Knorr et al. reported on a 24-week gestation newborn with congenital CMV infection presented on day 8 of life with hemophagocytic lymphohistiocytosis [40]. The treatment with granulocyte colony-stimulating factor and GCV was unsuccessful after 3 weeks since CMV pp65 antigen was detected in bone marrow and blood. Therapy with FOS at the dosage of 100 mg/kg/d and methylprednisolone (2 mg/kg/d) was started. After 8 d, the patient's neutrophil and platelet counts began to increase and normalization of platelets and

neutrophils was achieved following 3 weeks of treatment. Counts remained normal at the 18-month follow-up. No side effects were reported by Nigro and Knorr. Although there are no controlled studies in the neonatal population about possible efficacy of foscarnet for any herpes virus infections, foscarnet is considered as a second-line therapy (120 mg/kg/d IV in two divided doses) for neonatal neurological or disseminated HSV infection [34].

Cidofovir

Cidofovir (CDV) (HPMPC, or 1-[(S)-3-hydroxy-2-(phosphonomethoxy)-propyl]cytosine dihydrate), a white crystalline powder with an aqueous solubility of $\geq$170 mg/mL at pH 6–8 and a log P (octanol/aqueous buffer, pH 7.1) value of -3.3, is a monophosphate nucleotide analog of cytosine. Like FOS, CDV is only available as an iv solution, at a concentration of 75 mg/mL. Once diphosphorylated to its active state, CDV acts to competitively inhibit incorporation of host deoxycytidine into the viral DNA by viral DNA polymerase [41]. Whereas GCV and acyclovir are modified as precursors of the active form of the drug by the CMV UL97 gene-induced phosphotransferase and by the thymidine kinase in herpes simplex virus infections, CDV is not subjected to phosphorylation by virally encoded enzymes [42]. Therefore, CDV can be used to treat patients infected with CMV isolates that have developed resistance to GCV through a UL97 mutation. The murine CMV model, which was extensively used for the evaluation of new anti-CMV compounds, showed that CDV had greater activity than GCV [42].

Pharmacokinetics and adverse effects

Like for FOS, PK data for CDV in children are extremely limited. Over 80% of the drug is excreted by kidneys unchanged within 24 h after administration. An active metabolite, CDV diphosphate, is eliminated more slowly, with a first intracellular phase $t_{1/2}$ of 24 h and a second intracellular phase of 65 h. Because of the slow elimination, CDV can be administrated every 2 weeks. Breddemann et al. evaluated the PK properties of CDV in the pediatric cancer patients derived from the analysis of the concentration–time profile [43] (Table 1). The maximal concentration level after a CDV dose of 2.5 mg/kg was 4.62 μg/mL, with an AUC of 9.07 μg/h/mL, a volume distribution of 560 mL/kg and a Cl of 257 mL/h/kg.

Clinical effects

Bravo et al. reported that oral hexadecyloxypropyl-cidofovir (HDP-CDV) therapy in pregnant guinea pigs improves outcome in the congenital model of CMV infection, showing potential as a well-tolerated anti-viral candidate for treatment of congenital human CMV infection [44]. All HDP-CDV regimens significantly improved pup survival, from 50 to 60% in control animals to 93 to 100% in treated animals ($p < 0.019$). Treatment with 20 mg/kg HDP-CDV significantly reduced the viral load in pup spleen ($p < 0.017$) and liver ($p < 0.029$). Virus levels in the placenta were significantly reduced at 10 dpi following daily treatment with 4 mg/kg HDP-CDV for 5 or 9 d. The 9-d treatment also significantly reduced the viral levels in the dam spleen and liver. Schleiss et al. first evidenced that CDV prevents congenital CMV infection in a guinea pig model [45]. Pregnant outbred Hartley guinea pigs were challenged in the early-third trimester with guinea pig CMV (GPCMV) and treated with placebo or the anti-viral agent, cyclic cidofovir (cHPMPC). The rate of GPCMV-induced maternal and fetal mortality in this study was reduced from 5/25 animals in the placebo group to 0/21 animals in the treatment group ($p = 0.05$). By viral culture assay, anti-viral therapy was found to completely prevent GPCMV transmission to the fetus. In control pups, 5/19 (26%) were culture positive for GPCMV, compared to 0/16 of pups in the cyclic cidofovir treatment group ($p < 0.05$). In 25 kidney transplanted children, Florescu et al. recently reported a marginal decreased median change in the creatinine from baseline to 1 month after CDV treatment ($p = 0.06$) [46]. Fewer patients had proteinuria (72.2% versus 27.8%; $p = 0.02$) and hematuria (22.2% versus 0%) after CDV. However, more patients were receiving renal replacement therapy (RRT) while treated with CDV compared with baseline (24% versus 4%; $p = 0.03$). They concluded that CDV did not significantly change renal function reflected by creatinine, GFR, hematuria or proteinuria, but a significant number of patients required RRT because of fluid overload. No data are reported in literature about the treatment of congenital CMV infection resistant to GCV or FOS. CDV is currently approved for the treatment of CMV retinitis in AIDS patients, but the spectrum of its therapeutic use also includes the pre-emptive therapy and the treatment of disease in CMV-infected pediatric cancer patients. The most common side effect of CDV is renal impairment, which was reported by clinical trials in approximately 50% of adults [41].

Concluding remarks

Congenital CMV infection is very common throughout the world, since CMV is highly placentotropic and maternal–fetal transmission may follow both primary and recurrent maternal infection. Because the consequences may be severe immediate or late sequelae, mostly neurologic or auditory, the need for anti-viral therapies in infants and neonates is growing. None of the currently four anti-virals available, GCV, val-GCV, FOS, and CDV, have approved indications for use in children. While there are limited data regarding the dose, PKs, safety, and adverse events for FOS and CDV, GCV, and its oral pro-drug val-GCV, have been the best studied anti-viral drugs in the infant and neonate populations. The volume of distribution, clearance, and half-life of GCV, when normalized for weight, are similar to those of the adults. Neutropenia is the most frequent side effect associated with GCV and val-GCV, whereas significant renal toxicity can occur during CDV therapy. FOS administration can also result in renal toxicity as well as significant electrolyte imbalances. Potential toxicities of GCV, val-GCV, and CDV, observed in animal studies, include carcinogenesis, teratogenesis, and reversible azospermia. However, val-GCV appears to be the most reliable anti-CMV drug, given the favorable results which can be obtained using prolonged administration and the low rate of side effects in full-term immunocompetent infants.

Declaration of interest

The authors declare that they have no competing interests.

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