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SHORT REPORT

Sven Schulzke · Christoph Bührer

Valganciclovir for treatment of congenital cytomegalovirus infection

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Abbreviations CMV: Cytomegalovirus · HIV: Human immunodeficiency virus · ANC: Absolute neutrophil counts · PCR: Polymerase chain reaction

Ganciclovir, administered via an intravenous central line over 6 weeks to newborn infants symptomatically infected with cytomegalovirus (CMV), has been shown to prevent progressive disease, as gauged by less hearing deterioration, in a randomized phase III trial [2]. However, almost two-thirds of treated infants have significant neutropenia during therapy, and some get infections related to indwelling intravenous catheters [2, 3]. The valine ester of ganciclovir, valganciclovir, is an orally applicable prodrug successfully used in transplant recipients and human immunodeficiency virus (HIV) patients. Bioavailability of ganciclovir from oral valganciclovir has been reported to be about 60% in adults and 43% in a 6-year-old child [1] while it has been difficult to attain stable ganciclovir serum levels with oral valganciclovir in a newborn infant as was recently published [4].

We report on a term newborn girl with symptomatic CMV infection presenting with hepatosplenomegaly, "blueberry muffin" rash, thrombocytopenia, elevated liver enzymes, lenticulostriate vasculopathy, periventricular calcifications, partial polymicrogyria, and severe hearing impairment (hearing thresholds 100 and 120 dB). She tested positive for anti-CMV IgG and IgM, and CMV was detected in urine and blood by culture and polymerase chain reaction (PCR).

On day 4 of life, ganciclovir was started via central venous access as described [2]. While the rash and hepatosplenomegaly resolved completely, there was progressive anemia (nadir of hemoglobin 7.8 g/dl) treated with oral iron. Platelet counts dropped to 26,000/μl immediately prior to start of ganciclovir but recovered quickly thereafter, remaining above 200,000/μl. However, intravenous ganciclovir was reduced and eventually discontinued when her absolute neutrophil counts (ANC) dropped <500/μl (Table 1). The central line was removed, and after informed parental consent and notification of the Swiss federal healthcare authority, oral treatment with valganciclovir (Valcyte, Roche, Switzerland) was commenced as soon as ANC rose to 540 cells/μl at 20 days of life. Oral valganciclovir was incrementally increased up to 56 mg/kg per day as long as ganciclovir serum trough levels were <1 mg/l and ANC >1,000/μl. This regimen did not result in relapse of neutropenia, while CMV viral load fell below the detection limit of 600 copies/ml (Table 1). Valganciclovir was discontinued after a total of 6 weeks on medication [2]. No further side effects were noted. For the last 4 weeks, she was seen as an outpatient. When last examined at 9 months of age, she was well, equipped with hearing aids, and being evaluated for cochlear implants.

Thus, substituting oral valganciclovir for intravenous ganciclovir in term newborn infants is feasible, resulting in ganciclovir serum concentrations in the range associated with CMV control [6], eventual suppression of CMV viremia, and significant cost savings, as much of the therapy can be done on an outpatient basis. In addition, it allows for studies aiming at extending the time of administration beyond 6 weeks [4] and also including not overtly symptomatic infants with congenital CMV infection [5]. However, the complex relationship between valganciclovir dose and serum levels in this and the only other report so far [4] points to the need for prior pharmacokinetic studies.

S. Schulzke · C. Bührer (✉)
Department of Neonatology,
Universitäts-Kinderspital beider Basel,
4005 Basel, Switzerland
e-mail: christoph.buehrer@ukbb.ch
Tel.: +41-61-2659565
Fax: +41-61-2659568

Table 1 Absolute neutrophil counts (ANC), ganciclovir plasma trough levels (kindly measured by Dr. M. Oellerich, Göttingen, Germany) and CMV plasma loads (kindly determined by Dr. K. Hamprecht, Tübingen, Germany) in the newborn infant with symptomatic congenital CMV infection sequentially treated with intravenous ganciclovir and oral valganciclovir

Aged (days)	ANC cells/μl	Ganciclovir dose (mg/kg per day)	Valganciclovir dose mg (mg/kg per day)	Ganciclovir plasma trough level (mgl/l)	CMV plasma load (copies/ml)
1	3,195				
4	880	2×12 (9.2)			
7	825	2×12 (9.7)		0.26	
15	517	2×6 (4.5)		0.64	1,715
18	442	–	–		
20	540		2×18 (12.8)		
24	528		2×18 (12.4)	1.33	671
29	998		2×18 (12.0)	0.41	
31	1596		2×38 (24.9)		
38	1541		2×80 (49.4)		
43	956		2×100 (58.9)	0.97	<600
50	1400		2×100 (56.0)	0.80	<600

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