

Letter to the Editor

Therapeutic Drug Monitoring of Ganciclovir Treatment for Cytomegalovirus Infections Among Immunocompromised Children

To the editor—Ganciclovir is a first-line agent for the treatment of human cytomegalovirus (CMV); however, its pharmacokinetics are highly variable, which confounds efforts to consistently achieve therapeutic exposure with standard dosing regimens [1]. The results of therapeutic drug monitoring in adult solid organ transplant recipients receiving prophylaxis indicated that a 24-hour ganciclovir area under the curve (AUC₂₄) of 40–50 µg·hr per mL was associated with delayed development of CMV viremia [2]. However, the optimal exposure for the treatment of CMV disease is unknown. Here, we describe our experience using therapeutic drug monitoring in the treatment of CMV with ganciclovir in a child with a history of leaky severe combined immunodeficiency syndrome requiring hematopoietic stem cell transplantation with an AUC₂₄ target extrapolated from the adult literature.

A 4-year-old girl with a history of leaky severe combined immunodeficiency developed CMV viremia that was treated with foscarnet and briefly achieved virologic suppression. However, several weeks later, she was readmitted to the hospital with new symptoms of gastroenteritis and a plasma CMV load of 3.8 log₁₀IU/mL. CMV-resistance testing revealed a T813S mutation in the DNA polymerase gene (*UL54*), which can confer resistance to foscarnet, ganciclovir, and cidofovir [3]. Foscarnet was discontinued, and intravenous ganciclovir was initiated at 5 mg/kg twice daily.

Despite 4 weeks of ganciclovir induction therapy, her CMV load continued to rise. The clinical pharmacology service was consulted, and trough, peak, and 2 random blood samples were obtained for ganciclovir quantitation (Mayo Medical Laboratories, Rochester, Minnesota). The ganciclovir AUC₂₄ was calculated to be 32.9 µg·hr per mL, which, on the basis of adult prophylaxis studies [2], was approximately 65% of the desired exposure. To achieve an estimated AUC₂₄ of >50 µg·hr per mL, we shortened the ganciclovir dosing interval to 8 hours. The patient's CMV load declined from a peak of 4.2 log₁₀IU/mL on day 12 to below the limit of detection (<2.1 log₁₀IU/mL) at the time of discharge on day 53. Two weeks after discharge, her ganciclovir dosing interval was increased to 12 hours and then to 24 hours. Secondary prophylaxis was stopped 6 weeks after discharge. Her CMV has remained undetectable for 12 months.

Identifying safe and effective ganciclovir dosing regimens for children with CMV is challenging because of the scarcity of published pediatric reports and high between- and within-subject pharmacokinetic variability. We adopted a target AUC₂₄ of 50 µg·hr per mL, which was derived from a study conducted among 226 adult solid organ transplant recipients receiving prophylaxis who were evaluated 100 days after their transplant [2]. An AUC₂₄ of 50 µg·hr per mL was associated with an average incidence of CMV viremia of 1.3%, whereas an AUC₂₄ of 25 µg·hr per mL was associated with an 8-fold higher risk [2].

Recently, Padullés Caldés et al [4] developed a population pharmacokinetic model for adult solid organ

transplant recipients receiving ganciclovir for the treatment of CMV disease. The authors used this model and a Bayesian approach to evaluate 20 sampling strategies. The sampling design with the lowest bias and best precision included the collection of 3 samples 0.5–1.5, 4–5, and 6–8 hours after the start of the ganciclovir infusion. These optimal sampling windows may be considered for future studies that investigate pediatric AUC₂₄-based therapeutic drug monitoring for ganciclovir.

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