Therapeutic Drug Monitoring of Ganciclovir: Where Are We?

Anne-Grete Märtson, MSc,* Angela E. Edwina, MSc,* Hannah Yejin Kim, PhD,†‡§ Marjolein Knoester, PhD,* Daan J. Touw, PhD,*∥ Marieke G. G. Sturkenboom, PhD,* and Jan-Willem C. Alffenaar, PhD†‡§

Background: Ganciclovir is the mainstay of therapy for the prophylaxis and treatment of Cytomegalovirus. However, therapy with this antiviral agent is hindered by side effects such as myelosuppression, which often leads to therapy cessation. Underdosing, as an attempt to prevent side effects, can lead to drug resistance and therapy failure. Therapeutic drug monitoring (TDM) has been used to overcome these problems. The purpose of this narrative review was to give an overview of ganciclovir TDM, available assays, population pharmacokinetic models, and discuss the current knowledge gaps.

Methods: For this narrative review, a nonsystematic literature search was performed on the PubMed database in April 2021. The following search terms were used: ganciclovir, valganciclovir, pharmacokinetics, pharmacodynamics, population pharmacokinetic, therapeutic drug monitoring, bioassay, liquid chromatography coupled with tandem mass spectrometry, liquid chromatography, spectrophotometry, and toxicity. In addition, the reference lists of the included articles were screened.

Results: The most common bioanalysis method identified was liquid chromatography coupled with tandem mass spectrometry. There are different models presenting ganciclovir IC50; however, establishing a pharmacokinetic/pharmacodynamic target for ganciclovir based on preclinical data is difficult because there are no studies combining dynamic drug exposure in relation to inhibition of viral replication. The data on ganciclovir TDM show large interindividual variability, indicating that TDM may play a role in modifying the dose to reduce toxicity and prevent treatment failure related to low concentrations. The main hurdle for implementing TDM is the lack of robust data to define a therapeutic window.

Conclusions: Although the pharmacokinetics (PK) involved is relatively well-described, both the pharmacodynamics (PD) and pharmacokinetic/pharmacodynamic relationship are not. This is because the studies conducted to date have mainly focused on estimating ganciclovir exposure, and owing to the limited therapeutic options for CMV infections, future studies on ganciclovir are warranted.

Key Words: ganciclovir, valganciclovir, therapeutic drug monitoring, cytomegalovirus

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INTRODUCTION

Cytomegalovirus (CMV) is a major complication in immunocompromised patients, particularly in hematopoietic stem cell transplant (HSCT) and solid-organ transplant (SOT) recipients.1 Ganciclovir is the mainstay of therapy for the prophylaxis and treatment of CMV in SOT recipients.2,3 Ganciclovir, or 9-(1,3-dihydroxy-2-propoxymethyl)guanine, is a cyclic analog of the endogenous purine nucleoside guanosine.4 Ganciclovir is administered intravenously, whereas the prodrug valganciclovir is administered orally and gets hydrolyzed to ganciclovir postabsorption (bioavailability of a single dose of valganciclovir is approximately 60%).5 The antiviral activity of ganciclovir requires intracellular phosphorylation and activation by the UL97 viral kinase and UL54 DNA polymerase. Ganciclovir monophosphate is further phosphorylated to ganciclovir triphosphate by cellular kinases and inhibits CMV DNA polymerase6–10 (Fig. 1). Once ganciclovir triphosphate is formed, it seems to be very stable and persists in CMV-infected cells for several days, with an intracellular half-life (t1/2) of 16.5 hours.5

For the treatment of CMV in both SOT and HSCT, intravenous (IV) ganciclovir at a dose of i.v. 5 mg/kg or oral
valganciclovir at a dose of p.o. 900 mg twice daily is the recommended regimen in adults with normal renal function. Viral load thresholds at which the treatment is started may differ depending on the risk profile and immune status of the patients. To prevent CMV infection or reactivation after SOT, prophylaxis is recommended depending on the donor and recipient CMV IgG status and the transplanted organ. Regarding donor and recipient CMV IgG status, the risk of CMV complications is, for example, highest if the recipient is seronegative and the donor is seropositive and lowest when both are negative. Transplants for which higher immunosuppressive regimens are needed (eg, lung transplantation) pose a higher risk of CMV reactivation than those that require less immunosuppression (eg, liver transplantation). Duration of prophylaxis may range from 3 to 12 months.

Ganciclovir toxicity can cause myelosuppression, that is, neutropenia, thrombocytopenia, and leukopenia, which can lead to dosage changes or cessation of therapy. The rate of myelotoxicity varies between the specific patient groups. In HSCT, the rates seem to be 50% and higher, whereas in SOT, much lower rates of approximately 10% have been reported. Therefore, pre-emptive treatment is mostly used after HSCT to avoid the side effects of (val)ganciclovir. In pre-emptive treatment, the treatment is initiated when CMV is detected by routine monitoring but before the onset of symptoms. Granulocyte colony–stimulating factor has been used to manage the myelotoxicity caused by ganciclovir. However, the occurrence of myelotoxicity can lead to a clinician-directed dose reduction. By contrast, ganciclovir underexposure can lead to viral drug resistance, which is caused by mutations in the UL97 and UL54 genes

![FIGURE 1. Antiviral mechanism of ganciclovir.](Image)

**METHODS**

For this narrative review, a nonsystematic literature search was performed on the PubMed database in April 2021. The following search terms were used: ganciclovir, valganciclovir, pharmacokinetics, pharmacodynamics, population pharmacokinetics, therapeutic drug monitoring, bioassay, LC-MS/MS, liquid chromatography, chromatography, spectrophotometry, and toxicity. In addition, the reference lists of the included articles were screened.

**BIOANALYSIS**

A number of assay procedures using high-performance liquid chromatography and ultra-high–performance liquid chromatography (UPLC) with detectors, such as mass spectrometry, fluorescence spectrophotometry, diode array detectors, UV spectrophotometry, and pulsed amperometers, have been developed to quantify ganciclovir concentrations in biological matrices, especially serum and plasma. A total of 14 liquid chromatographic methods with various detection methods are summarized in Table 1. Six studies described the development of liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). One study used capillary electrophoretic methodology, whereas another used Raman spectroscopy to detect ganciclovir after ocular administration.

LC-MS/MS is the preferred method to quantify ganciclovir concentrations because of its high sensitivity, selectivity, and simple sample pretreatment, especially when stable isotopes of ganciclovir are used as an internal standard. The ideal assay should have the ability to quantify ganciclovir concentrations in the concentration range that can be expected in patients [from the trough ($C_{\text{min}}$) to the peak ($C_{\text{max}}$) concentration].

According to the summarized studies, run times of ganciclovir assays ranged from 2.5 to 15 minutes. Shorter run times are desirable for the efficient use of the equipment. The LC-MS/MS method developed by Singh et al resulted in a run time of 2.5 minutes. A short run time of 2.5 minutes can also be obtained using the UPLC-UV assay developed by Padullès et al and UPLC-MS/MS assay developed by Rigo-Bonnin et al. The reduction in retention time was aided not only by the intrinsic time of the instruments but also by the implementation of an isocratic program that avoids the time taken to re-equilibrate the chromatographic system.

Twelve of the 14 summarized studies conducted ganciclovir stability testing in plasma or serum. Plasma samples were stable at room temperature for 16–24 hours, whereas serum samples stored...
| Author, Year | Analytes | Instrument | Detection | Sample | Run Time | LLOQ and/or LOD (mg/L) | Stability Testing |
|--------------|----------|------------|-----------|--------|----------|-----------------------|------------------|
| Chan et al, 1998 | Ganciclovir | HPLC | Spectrophotometer (λ<sub>ex</sub> = 278 nm; λ<sub>em</sub> = 380 nm) | Serum and heparinized human plasma | ≤15 min | 0.04 | 4°C for 0, 24, and 48 h; 22°C for 0, 24, and 48 h |
| Merodio et al, 2000 | Ganciclovir | HPLC | Diode array λ = 254 nm | Albumin nanoparticles; human corneal fibroblasts | 8 min | 0.05 | 4°C for 1 mo; −20°C for at least 3 mo |
| Tsuchie et al, 2001 | Ganciclovir | HPLC | Spectrophotometer (λ<sub>ex</sub> = 365 nm; λ<sub>em</sub> = 512 nm) | Human serum | 7.4 min (retention time) | 0.005 (LOD) | — |
| Kishino et al, 2002 | Ganciclovir | HPLC | Pulsed amperometer | Plasma samples from transplant recipients | 6.26 min | 0.01 (LOD), 0.05 (LLOQ) | −20°C for 1 mo |
| Hosseini et al, 2002 | Ganciclovir | Electrophoresis | Raman spectrometer | Rabbit eye | — | — | — |
| Saleh and Hempel, 2006 | Ganciclovir | UPLC | UV | Human plasma | — | 0.5 | — |
| Perrotet et al, 2007 | Ganciclovir | HPLC | Spectrophotometer (λ<sub>ex</sub> = 260 nm; λ<sub>em</sub> = 380 nm) | Plasma from SOT patients receiving valganciclovir as prophylaxis | 13 min (retention time) | 0.1 | —20°C for at least 4 months; room temperature up to 24 h |
| Xu et al, 2007 | Valganciclovir, ganciclovir | LC-MS/MS | Tandem mass spectrometer | Human plasma | 5.5 min | 0.004 (valganciclovir), 0.1 (ganciclovir) | 3 freeze-thaw cycles; room temperature for 4 h |
| Weller et al, 2008 | Ganciclovir | HPLC | UV | Plasma | 8 min | 0.05 | 4°C for 7 d; 23°C × 24 h; 5 freeze-thaw cycles |
| Singh et al, 2011 | Ganciclovir, valganciclovir | LC-MS/MS | Tandem mass spectrometer | Human plasma | 2.5 min | 0.005 | −20°C and −50°C for 86 d; 3 freeze-thaw cycles stability, bench top stability (25°C) for 16 h, autosampler stability (1–5°C) for 54 h |
| Padullés et al, 2012 | Ganciclovir | UPLC | UV λ = 254 nm | Human plasma | 2.5 min | 0.5 | −20°C for 24 h and 3 mo |
| Rigo-Bonnin et al, 2014 | Ganciclovir | UPLC-MS/MS | Tandem mass spectrometer | Plasma | 2.5 min | 0.06 (LLOQ), 0.03 (LOD) | 5°C for 7 d; 4°C for 24 h; −75°C for 6 mo |
| Billat et al, 2015 | Ganciclovir and its derivatives in cells | LC-MS/MS | Tandem mass spectrometer | Whole blood healthy volunteers | — | — | At 4°C for 24 h |
| Gunda et al, 2015 | Ganciclovir, valganciclovir, tyrosine-valganclovir | LC-MS/MS | Tandem mass spectrometer | Rat plasma samples | <3.8 min | 0.0005 (ganciclovir), 0.01 (valganciclovir), 0.01 (tyrosine valganclovir) | — |
| Märtson et al, 2018 | Ganciclovir | LC-MS/MS | Tandem mass spectrometer | Human serum | 4.5 min | 0.1 | 20–25°C for 144 h; 4°C for 144 h; 10°C for 120 h; −20°C for 1 yr |
TABLE 1. (Continued) Characteristics of the Evaluated Assays for the Determination of Ganciclovir and Its Derivatives

| Author, Year | Analytes           | Instrument        | Detection            | Sample                | Run Time | LLOQ and/or LOD (mg/L) | Stability Testing          |
|--------------|--------------------|-------------------|----------------------|-----------------------|----------|------------------------|---------------------------|
| Rower et al 2020 | Ganciclovir | LC-MS/MS | Tandem mass spectrometer | Dried blood spot from infants | 2.4 min (retention time) | 0.01 | −20°C and −80°C for 1 yr; room temperature for 16 h; autosampler (4°C) for 7 d |

HPLC, high-performance liquid chromatography; LLOQ, lower limit of quantification; LOD, lower limit of detection; UPLC, ultra-high-performance liquid chromatography; UV, ultraviolet.

at room temperature were stable for up to 144 hours.\(^{36}\) In addition, ganciclovir in manelonic stock solution can be stored for up to 1 year at a temperature of −20°C.\(^{36}\) Ganciclovir in plasma stored at −20°C or −50°C was stable for 86 days.\(^{33}\) After 5 freeze–thaw cycles, plasma ganciclovir concentrations remained stable.\(^{30}\)

Rower et al\(^{37}\) successfully developed and clinically validated an assay to analyze dried blood spots (DBSs), which were extracted using a simple methanol sonication. They confirmed that ganciclovir concentrations in DBSs were similar, correlated well with those observed in serum, and were useful for describing the PK of ganciclovir. Generally, DBS is increasingly being used as an attractive sample for TDM because it offers the benefits of less invasive sample procurement and requirement of low sample volume, which also facilitates transport.\(^{41}\) Furthermore, it is feasible to perform home sampling with DBS, which would reduce the need for patients to travel to a blood collection site for TDM. The challenges with DBS are impact of spot volume, hematocrit, punch location, and blood collection site on blood volume and uniformity of drug distribution within a DBS punch and clinical validation of the DBS.\(^{42}\) The assay by Rower et al\(^{37}\) minimized the effect of spot volume and hematocrit during validation. However, the influence of blood collection sites on ganciclovir assay was not analyzed in this study because all samples were collected using venipuncture.

PRECLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS

Few studies have evaluated the in vitro activity of ganciclovir against CMV. Most models use human embryonic lung or foreskin fibroblast cells, with CMV AD169 as a reference strain. Antiviral activity is expressed in most models as the inhibitory concentration required to reduce viral replication by 50% (IC\(_{50}\)). Snoeck et al\(^{43}\) and Cai et al\(^{44}\) reported an IC\(_{50}\) of 0.6–1.6 mg/L\(^{43}\) and 0.13–0.2 mg/L\(^{44}\), respectively, whereas Freitas et al\(^{45}\) reported an IC\(_{50}\) of 0.9 mg/L (range, 0.6–1).\(^{45}\) When 42 clinical isolates were evaluated by Balfour et al,\(^{46}\) a mean IC\(_{50}\) of 1.7 μmol/L (range, 0.2–5.3 μmol/L) was observed. When mice were infected with CMV and ganciclovir was evaluated at doses of 1, 3, 9, and 27 mg/kg per day, the median effective dose (ED\(_{50}\), amount of drug that produces a therapeutic response in 50% of the subjects) was 6 mg/kg. In another study, a similar ED\(_{50}\) of 7 mg/kg was found in mice.\(^{47}\)

Similar to other pathogens, the selection of resistant mutants occurs over time when exposed to a drug. The same situation applies to CMV when exposed to ganciclovir.\(^{48}\) Chou et al\(^{49}\) tested the IC\(_{50}\) of 20 strains with a mutation in the UL97 gene and found an IC\(_{50}\) of >0.7 mg/L (range, 0.8–5.8).\(^{49}\) Some in vitro studies have also reported the inhibitory concentration required to reduce viral replication by 90% (IC\(_{90}\)). Balfour et al\(^{46}\) reported a mean IC\(_{90}\) of 0.3 mg/L (range, 0.1–1).\(^{46}\) IC\(_{90}\) may be a more clinically relevant concentration than the IC\(_{50}\) because it better reflects what is aimed for during treatment. Nokta et al\(^{50}\) showed that 53% inhibition was observed at a concentration of 0.3 mg/L, 74% inhibition at 1.2 mg/L, and 96% inhibition at 3.5 mg/L.\(^{50}\) Audrey et al used mathematical modeling to analyze the effect of ganciclovir on viral replication.\(^{51}\) Viral replication was completely inhibited at 20 mg/L, but when balancing efficacy and toxicity, a concentration of 10 mg/L was proposed to be optimal (normalized area under the concentration–time curve (AUC) of viable cells and normalized viral loads for 14 days). Establishing a pharmacokinetic/pharmacodynamic (PK/PD) target for ganciclovir based on preclinical data is difficult because there are no studies combining dynamic drug exposure in relation to inhibition of viral replication. This means that no clues are available on whether the efficacy is concentration-dependent or time-dependent. A potential solution could be to develop a hollow fiber infection model with planktonic fibroblast cells replicating CMV AD169. This could subsequently be exposed to ganciclovir using dose fractionation and could provide the first relevant data for identification of clinical targets.

CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS

The most common structural population PK model of ganciclovir in both adults and children is a 2-compartment model with lagged first-order absorption (oral administration) and elimination from the central compartment.\(^{10,52–59}\) A population PK model can be used to calculate the optimal dosing regimen for patients with different characteristics. According to the population PK models, ganciclovir dosing regimens should be based not only on creatinine clearance\(^{52,53,55,57–59}\) as a surrogate marker for renal function but also on body weight, transplant type, and sex.\(^{56}\) The population models are listed in Table 2.

The prodrug valganciclovir is rapidly hydrolyzed into ganciclovir after absorption.\(^{60}\) The time to maximum concentration (t\(_{\text{max}}\)) of ganciclovir after valganciclovir intake is 1.0–
| Author, Year | Software | Route of Administration or Formulation | Population (n), Country | Final Model |
|--------------|----------|---------------------------------------|-------------------------|-------------|
| Wiltshire et al, 200558 | NONMEM | Oral ganciclovir 1000 mg 3dd and valganciclovir 900 mg 1dd | SOT recipients aged 13 yr and older with a CMV serostatus of D+/R– (n = 364); United Kingdom | \( CL (L/h) = 12.4 \times (CL_{CR}\text{median})^{0.925} \times (WT/79.6)^{0.725} \) |
| | | | | \( CL_{CR} \text{ median males} = 80.4 \text{ mL/min} \) |
| | | | | \( females = 65.8 \text{ mL/min} \) |
| | | | | \( Vc (L) = 25 \) |
| | | | | \( Vp (L) = 49 \) |
| | | | | Inter-tissue CL (L/h) = 12 \( t_{lag} \) (h) = 0.883 |
| | | | | Ka (h⁻¹) = 0.128 |
| Chen et al, 202153 | NONMEM | Valganciclovir 450 mg and 900 mg 1dd | Adult kidney transplant recipients (n = 70); China | \( CL (L/h) = 7.09 \times (1 + CL_{CR}/68.3 \times 1.08) \) |
| | | | | \( Vc (L) = 10.8 \) |
| | | | | \( Q (L/h) = 3.96 \) |
| | | | | \( Vp (L) = 174 \) |
| | | | | Ka (L/h) = 0.23 \( t_{lag} \) (h) = 0.93 |
| Czock et al, 200254 | WinNonlin | Valganciclovir 900 mg 1dd | HIV-positive and CMV-positive patients (n = 32), healthy volunteers (n = 12); Germany and England | \( K_{10} \) (h⁻¹) = 0.022 |
| | | | | \( K_{12} \) (h⁻¹) = 1.44 |
| | | | | \( K_{21} \) (h⁻¹) = 0.66 |
| | | | | \( Vc (L/kg) = 0.213 \) |
| | | | | \( F = 0.63 \) \( t_{lag} \) (h) = 0.77 |
| | | | | \( t_{inpend} \) (h) = 5.5 |
| | | | | Khd (h⁻¹) = 0.57 |
| Zhao et al, 200959 | NONMEM | Valganciclovir 900 mg 1dd | Pediatric renal transplant recipients (n = 22); France | \( CL (L/h) = 8.04 \times (CL_{CR}/89)^{2.93} + 3.62 \times (WT/28) \) |
| | | | | \( Vc (L) = 5.2 \) |
| | | | | \( Vp (L) = 30.7 \) \( t_{lag} \) (h) = 0.743 |
| | | | | Ka (h⁻¹) = 0.369 |
| Franck et al, 202055 | NONMEM | Valganclovir 10 mg/kg 2dd and intravenous ganciclovir 5 mg/kg 2dd | Pediatric solid-organ and stem cell transplant recipients (n = 50); Canada | \( CL \times WT/26.7 \times CL_{CR}/149.8 (L/h) = 6.9 \) |
| | | | | \( Vc \times WT/26.7 (L) = 9.7 \) |
| | | | | \( Vp \times WT/26.7 (L) = 7.6 \) |
| | | | | Q \times WT/26.7 (L) = 10.9 \( t_{lag} \) (h) = 0.33 |
| | | | | Ka (h⁻¹) = 0.73 |
| | | | | F (%) = 43 |
| Vezina et al, 201457 | NONMEM | Valganciclovir 900 mg 1dd | Pediatric and adult SOT recipients (n = 82 adults and 13 children); USA | \( CL/F (L/h) = 14.5 \times (CL_{CR}/60)^{0.492} \times (WT/70)^{0.75} \) |
| | | | | \( Vc/F (L) = 87.5 \times (WT/70) \) |
| | | | | \( Vp/F (L) = 42.6 \times (WT/70) \) |
| | | | | Q/F (L/h) = 4.8 \times (WT/70)^{0.75} |
| Perrotet et al, 200956 | NONMEM | Valganclovir 900 mg 2dd (therapy), 900 mg 1dd (prophylaxis), 450 mg 1dd (renal impairment), and intravenous ganciclovir 5 mg/kg 2dd | Adult SOT recipients (n = 65); Switzerland | \( CL (L/h) = \theta_{\text{GraftType}} \times GFR_{\text{MDRD}} \times \theta_{\text{female}} \) |
| | | | | \( \theta_{\text{kidney}} = 1.68 \) |
| | | | | \( \theta_{\text{heart}} = 0.86 \) |
| | | | | \( \theta_{\text{lung/liver}} = 1.17 \) |
| | | | | \( \theta_{\text{female}} = 1.21 \) |
| | | | | \( Vc (L) = 24 \times (WT/70 \text{ kg}) \times \theta_{\text{female}} \) |
| | | | | \( \theta_{\text{female}} = 0.78 \) |
| | | | | \( Vp (L) = 22 \) |
| | | | | \( Q (L/h) = 4.1 \) |
| | | | | \( F = 0.6 \) |
| | | | | Ka (h⁻¹) = 0.56 |
TABLE 2. (Continued) Ganciclovir Population Pharmacokinetic Models

| Author, Year | Software | Route of Administration or Formulation | Population (n), Country | Final Model |
|--------------|----------|----------------------------------------|--------------------------|------------|
| Caldes et al, 2009<sup>52</sup> | NONMEM | Valganciclovir 900 mg 1dd and intravenous ganciclovir 5 mg/kg 2dd | Adult SOT recipients (n = 21); Spain | CL (L/h) = 7.49 × (CLCR/57) |
| | | | | Vc (L) = 31.9 |
| | | | | Q (L/h) = 10.2 |
| | | | | Vp (L) = 32.0 |
| | | | | Ka (h<sup>−1</sup>) = 0.895 |
| | | | | F = 0.825 tlag (h) = 0.382 |
| Billat et al, 2016<sup>10</sup> | Pmetrics | Valganciclovir 900 mg 1dd and 450 mg 1dd (renal impairment) | Adult renal transplant recipients (n = 22); France | CL/F (L/h) = 0.58 |
| | | | | Vc/F (L) = 32 |
| | | | | Vp/F (L) = 40.17 |
| | | | | K<sub>12</sub> (h<sup>−1</sup>) = 0.016 |
| | | | | K<sub>13</sub> (h<sup>−1</sup>) = 72.96 tlag = 0.0735 |

CL, clearance; CLCR, creatinine clearance; WT, body weight; F, bioavailability; Ka, absorption constant; Khd, elimination from the central compartment by hemodialysis; Q, intercompartmental clearance; tmax, time of the end of drug input; tlag, lag time; Vc, central volume of distribution; Vp, peripheral volume of distribution; dd, daily dose.

3.5 hours.<sup>54,61–65</sup> The bioavailability of valganciclovir is 24%–56% higher in the fed condition than that in the fasted condition.<sup>56</sup> In addition, food delays the t<sub>max</sub> of ganciclovir after valganciclovir intake, especially at higher dosages, with the respective fasted and fed t<sub>max</sub> being 1–1.8 hours and 1.5–2 hours, respectively.<sup>56</sup> Plasma protein binding of ganciclovir is negligible (1%–2%) over the concentration range of 0.5–51 mg/L.<sup>9</sup>

Ganciclovir is eliminated mainly through the kidneys by glomerular filtration and active tubular secretion. In patients with normal renal function, i.e., ganciclovir is 90% unchanged when it is excreted in the urine.<sup>9</sup> Elimination of ganciclovir is biphasic, and both systemic and intercompartmental clearances have been estimated in various studies.<sup>10,52–59,67</sup> In patients with mild renal impairment, ganciclovir clearance is almost half of the clearance value in healthy subjects (CL/F 14.9 L/h vs. 24.2 L/h).<sup>54</sup> Similarly, the mean ganciclovir clearance in renal transplant patients is lower (CL 0.6 L/h) than that in other transplant recipients (CL mean 11.15 L/h).<sup>10,52,53,55,57–59,68,69</sup>

Apart from renal function, other factors may also affect ganciclovir elimination. Differences in drug regimens for specific transplantations (eg, immunosuppressives) may contribute to the variability in ganciclovir elimination.<sup>56</sup> Interestingly, female patients have a higher clearance than men, which may be associated with the sex differences in organic anion transporter expression observed in rodents.<sup>56,70,71</sup>

Currently, there are limited data available regarding the exposure targets to use to optimize therapy. In addition, the specific IC<sub>90</sub> that is related to the decrease in viral load in patients has not been confirmed. A target 24-hour area under the time concentration curve (AUC<sub>24h</sub>) of 40–60 mg·h/L has been proposed for prophylaxis.<sup>72,73</sup> Wiltshire et al described that an AUC of 40–50 mg·h/L was associated with a suppression of viral load during prophylaxis after 1 month; however, this was not seen after 6 months and they did not evaluate other PK parameters besides the AUC.<sup>73</sup> Stockmann et al suggested in an expert opinion that an AUC<sub>24h</sub> of 80–120 mg·h/L could be used as a potential efficacy target to treat CMV infections.<sup>72</sup> Although these AUC<sub>24h</sub> targets have been used to optimize therapy, no PK/PD index is available to improve efficacy and reduce toxicity.<sup>74</sup>

**THERAPEUTIC DRUG MONITORING**

There is an urgent need for optimization of ganciclovir dosing to avoid antiviral resistance and toxicity, especially in HSCT recipients.<sup>17,72,75</sup> Various case studies have presented TDM as a potential solution to optimize treatment in specific clinical scenarios.<sup>76–78</sup> Despite the lack of strong evidence to support TDM, multiple centers have started TDM programs.<sup>52,74,79–81</sup> In these studies, specific target ranges were defined. Ritchie et al used 1–3 mg/L for C<sub>min</sub> and 3–12.5 mg/L for C<sub>max</sub>, whereas Märtson et al defined AUC<sub>24h</sub> > 50 mg·h/L or C<sub>min</sub> of 1–2 mg/L for prophylaxis and 80–120 mg·h/L or 2–4 mg/L for treatment, respectively.<sup>74,79</sup> These targets were based on either expert opinions or calculations from the IC<sub>50</sub> of ganciclovir.

A retrospective study on ganciclovir TDM by Ritchie et al<sup>79</sup> reported 82 patients with CMV infection and observed large interindividual variability among them.<sup>79</sup> Moreover, 52% of these patients did not reach the predefined target ranges.<sup>79</sup> No relationship was found between drug exposure and treatment efficacy or toxicity.<sup>79</sup> Similarly, high interindividual and intraindividual variability was observed in a study performed in 95 transplant recipients, where patients on both prophylaxis and treatment of CMV and herpesvirus type 6 were included.<sup>74</sup>

It was also seen that even appropriate dosing results in underexposure in both the prophylaxis and treatment groups and that the AUC did not have a strong correlation with C<sub>min</sub> values.<sup>74</sup> This could mean that C<sub>min</sub> alone does not provide a good overview of ganciclovir exposure. In addition, underexposure was observed in patients with an estimated glomerular filtration rate (eGFR) > 90 mL/min/1.73 m<sup>2</sup>, which could be expected because of the PK of ganciclovir.<sup>74</sup> The decrease in white blood cell counts significantly correlated with the highest AUC and C<sub>min</sub> values, which could mean that toxicity could...
be suspected with higher concentrations and AUC values. Because of the observational nature of the study and lack of follow-up data, clinical outcomes could not be linked to ganciclovir exposure. In another recent study, 90 patients with CMV infection were evaluated during a 17-month study period.\textsuperscript{82} Although patients did not always receive a dose according to guideline, the study showed that with peak concentrations lower than 8.37 mg/L or higher than 11.86 mg/L, poorer outcomes were observed.\textsuperscript{82} Poor outcomes were defined as time to resolution of CMV, breakthrough CMV during prophylaxis, and cessation of therapy due to toxicity.\textsuperscript{82} The preclinical and clinical PK and PD, together with potential TDM applications, are shown in Figure 2.

In the pediatric population, underexposure and variability of concentrations have also been observed, and the application of the same AUC\textsubscript{24h} targets has been used; however, there is a need for more studies on children.\textsuperscript{72,80,83} Asberg et al proposed a new ganciclovir dosing algorithm in pediatric SOT recipients using nonparametric modeling, where they conducted Monte Carlo simulations to evaluate the new regimens.\textsuperscript{83} The algorithm included body weight and not body surface area. In addition, the renal function (eGFR) was estimated using the Cockcroft–Gault formula as opposed to the regularly used Schwartz formula in children.\textsuperscript{83} The model accurately predicted ganciclovir concentrations.

**DISCUSSION, GAP ANALYSIS, AND OUTLOOK**

(Val)ganciclovir therapy is complicated by frequently reported toxicities. The data on ganciclovir concentrations show large interindividual variability, indicating that TDM may play a role in modifying the dose to reduce toxicity and prevent treatment failure related to low concentrations. The main hurdle for implementing TDM is the lack of robust data to define a therapeutic window. Before TDM-guided
intervention studies can be performed, there is a need to better understand the relationship between ganciclovir exposure and the inhibition of viral replication by intracellular ganciclovir triphosphate. In addition to the PK/PD of ganciclovir, there is a need for a better understanding of the quantitative role of the immune response of the patient and exposure to different immunosuppressives in relation to viral clearance. Ho et al formulated that the interplay between PK, PD, and host immunity factors should be the focus of future research. Indeed, it is important to consider all these when designing studies for optimization of ganciclovir therapy because the studies conducted to date have mainly focused on estimating ganciclovir exposure, and owing to the limited therapeutic options for CMV infections, future studies on ganciclovir are warranted.

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