

Therapeutic Drug Monitoring of Ganciclovir in Cytomegalovirus-Infected Patients With Solid Organ Transplants and Its Correlation to Efficacy and Toxicity

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Background: Cytomegalovirus causes morbidity and mortality, especially in immunocompromised patients, and is treated with (val)ganciclovir. Therapeutic drug monitoring of ganciclovir is often performed; however, clinically established target trough levels corresponding to efficacy are lacking. In 2021, our clinic increased the target trough level for ganciclovir from 1 to 2 mg/L to 2–4 mg/L. This study aims to compare both target trough levels in efficacy, toxicity, and occurrence of resistance.

Methods: A retrospective cohort study was performed in adult solid organ recipients treated for cytomegalovirus infection with (val)ganciclovir. Clinical efficacy was defined as the absence of treatment failure, defined as $> 1 \log_{10}$ increase in viral load within 2 weeks of treatment initiation, therapy switch to foscarnet, and/or request for resistance analysis.

Results: A total of 46 patients were involved in the study, with 200 ganciclovir trough levels obtained. The composite endpoint was recorded in 23 (69.7%) and 10 (76.9%) patients in the 1–2 mg/L and the 2–4 mg/L group, respectively ($P = 0.18$). No association was found between ganciclovir trough levels and the composite endpoint ($P = 1.0$). However, a correlation was found between ganciclovir trough levels and the occurrence of lymphopenia ($P = 0.02$).

Conclusions: Our study could not establish a difference in clinical efficacy or toxicity between target trough levels of

1–2 mg/L or 2–4 mg/L because of the lack of clinical differences between the compared groups. However, a correlation was found between ganciclovir trough levels and lymphopenia, which warrants further investigation.

Key Words: therapeutic drug monitoring, ganciclovir, CMV infection, transplant patients

(*Ther Drug Monit* 2023;45:533–538)

INTRODUCTION

Cytomegalovirus (CMV) affects a large proportion of the general population without causing significant clinical symptoms. However, in patients having undergone solid organ transplantation, owing to immune suppression, the previously latent virus can reactivate and cause great morbidity and mortality.^{1,2}

Ganciclovir and its oral prodrug, valganciclovir, are currently used as first-line therapies for the prevention and treatment of CMV infection.^{3,4} Ganciclovir and its valine ester valganciclovir are nucleoside analogs of guanosine that inhibit viral replication by preventing the use of deoxyguanosine triphosphate by DNA polymerases to elongate the genetic chain.⁵ The most significant side effect of (val)ganciclovir is myelosuppression.

The pharmacokinetic properties of (val)ganciclovir are characterized by great interindividual variability in plasma levels. Therefore, therapeutic drug monitoring (TDM) is performed in numerous care facilities. However, clinically established target trough levels for efficacy or toxicity are lacking. Several studies have suggested an association between plasma levels and efficacy^{6–10} or toxicity^{11–15} and advocated for TDM, whereas others have not.^{11,16–21} In our hospital, target trough levels for ganciclovir of 1–2 mg/mL were used until March 1, 2021; thereafter, target trough levels of 2–4 mg/mL were used in accordance with Martson et al.² The main objective of our study was to determine whether these higher target trough levels resulted in higher efficacy in treating CMV infections in solid organ transplant patients. The secondary aim was to investigate whether there was a relationship between plasma levels and efficacy, toxicity, or the development of ganciclovir resistance.

METHODS

Design and Patient Population

This retrospective, single-center cohort study was conducted at the University Medical Center in Utrecht using

Received for publication August 11, 2022; accepted October 6, 2022.

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The authors declare no conflict of interest.

All contributing authors have read and agreed upon the current manuscript. No other contributors met the authorship criteria. No approval from an ethics committee was needed since retrospectively gathered data were used for this research.

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data retrieved from electronic medical records from January 2012 to January 2022.

Adult patients who had undergone a solid organ transplantation and were treated for CMV infection with (val)ganciclovir, and from whom at least 1 ganciclovir trough level (as part of routine care) and 2 CMV viral loads were examined were included in the study. Primo infection and reactivation, with or without systemic symptoms and organ damage were considered relevant for the study, with classification according to the criteria by Ljungman et al.²² In our center, the duration of prophylaxis differed between recipients of heart, kidney, and lung transplants (3, 6, and 6–12 months, respectively).

Serum ganciclovir concentrations were determined using liquid chromatography coupled with mass spectrometry (LC-MS/MS). This assay uses ganciclovir-d5 as an internal standard and has proven linearity in the range of 0.2–15 mg/L. The lower limit of quantification was set at 0.2 mg/L, and the within-run and between-run precision at a concentration of 3.0 mg/L was 5.0% and 6.0%, respectively. Plasma levels were considered trough levels if they were obtained at most 60 minutes before the next administration. The trough levels were interpreted by hospital pharmacists, who made the dose adjustment recommendations. CMV viral loads in the plasma were determined using quantitative polymerase chain reaction based on a real-time TaqMan CMV-DNA polymerase chain reaction assay, as described previously.²³ Resistance analysis was performed by sequence analysis of the UL54 and UL97 genes.

The following data were collected: patient characteristics (sex, age, underlying disease, type of transplant, and need for and type of renal replacement therapy), disease and treatment specifics (indication according to disease criteria by Ljungman et al,²² administration route), and laboratory values (hemoglobin, white blood count, platelet, neutrophils and lymphocyte count, creatinine, and estimated glomerular filtration calculated with CKD-EPI) to determine the frequency of adverse effects using criteria for nephrotoxicity²⁴ and myelotoxicity.²⁵

Study Endpoints

The primary endpoint was the difference in efficacy between target trough levels. At our center, a target trough level of 1–2 mg/L was originally used; however, from March 1, 2021 onward, trough levels of 2–4 mg/L were deemed adequate according to the study by Martson et al.² This made it possible to compare the patients treated before and after March 1, 2021.

Efficacy was defined as the absence of treatment failure for which a composite endpoint was formulated: > 1 log₁₀ rise in viral load,²⁶ therapy switch to foscarnet (due to insufficient efficacy of ganciclovir, not because of side effects), and/or request for resistance analysis. This composite endpoint was chosen because the decline in viral load is dependent on multiple factors, such as underlying and concomitant diseases and degree of immune suppression, and does not reflect treatment success alone. When physicians doubt whether the treatment will be successful, a switch to foscarnet or resistance analysis is often considered, and this was therefore used to measure efficacy in this study.

Secondary endpoints were taken to be the association between trough levels and efficacy, toxicity, occurrence of

resistance (21), and difference in time to reach viral decay (viral load <100 IU/mL) in different target trough level groups.

Statistical Analysis

For data collection and analysis, SPSS (IBM SPSS Statistics 28, Armonk, NY) and R (4.1.2.) were used. Population and TDM characteristics were summarized as descriptive statistics (mean and SD (SD), median and interquartile ranges (IQR), frequencies, and percentages).

To compare the efficacy between the target trough levels, the χ^2 and Fisher exact tests were used for categorical data. Numerical data were compared using the *t* test for normally distributed data and Wilcoxon rank test for non-normally distributed data.

To determine the association between the composite endpoint and toxicity, repeated measures of ganciclovir levels were used to construct a general estimating equation (GEE) model. Independent correlations were also used. Because more frequent repeat measures are expected in patients who have low trough levels, interactions between the composite endpoint and time between trough level measurements were allowed to minimize confounding because of this phenomenon. The baseline viral load was also included in the model because previous studies have shown slower viral decay at higher baseline viral loads.²⁶

Kaplan–Meier survival curves and a Cox regression model (with age, type of transplant, baseline viral load, and baseline kidney function as covariates) were constructed to assess differences in time taken for viral decay in patients with different target trough levels. Proportional hazard assumptions were tested using scaled Schoenfeld residuals and their independence over time. *P* values below 0.05 were deemed statistically significant.

RESULTS

Patient and TDM Characteristics

A total of 46 patients were enrolled, of whom 28 had undergone kidney transplantation, 11 had undergone lung transplantation, and 7 had undergone heart transplantation. The patients' characteristics are listed in Table 1. Most patients had (val)ganciclovir prescribed for CMV infection (65.2%), 26.1% for CMV syndrome, and the remaining 8.7% for CMV disease. The patient characteristics did not differ significantly between the 2 different target trough level groups.

Overall, 200 trough levels were obtained, with a median of 3 (IQR 2.0–5.8) per patient. The median (IQR) of the first obtained through level was 1.4 (0.7–2.0) mg/L for all patients. When divided as per patients who were treated per used target trough levels (1–2 mg/L versus 2–4 mg/L), they were 1.6 (0.8–2.0) mg/L and 1.1 (0.7–1.6) mg/L, respectively (*P* = 0.76).

The median (IQR) for all trough levels was 1.7 (0.9–1.9) for patients with 1–2 mg/L target trough levels and 1.5 (1.2–1.9) for those with 2–4 mg/L target trough levels (*P* = 0.74).

TABLE 1. Patient Characteristics

Variable	Total n = 46	1-2 mg/L Target Trough Level Group (n = 36)	2-4 mg/L Target Trough Level Group (n = 10)	P
Age (yr) mean ± SD	56 ± 14.4	54.6 ± 15.4	60.6 ± 9.5	0.42*
Female n (%)	21 (45.7)	18 (50.0)	3 (30.0)	0.30†
Type of transplant n (%)				0.55†
Kidney	28 (60.9)	21.0 (58.3)	7.0 (70.0)	
Lung	11 (23.9)	9.0 (25.0)	2.0 (20.0)	
Heart	7 (15.2)	6.0 (16.7)	1.0 (10.0)	
CMV status [~] n (%)				0.88†
Infection	30 (65.2)	23.0 (63.8)	7.0 (70.0)	
Syndrome	12 (26.1)	10.0 (27.8)	2.0 (20.0)	
Disease	4 (8.7)	3.0 (8.3)	1.0 (10.0)	
CMV load at baseline (IU/mL); median (IQR)	9,82E±3 (1,47E±3–6,31E±4)	1,07E±3 (1,39E±3–4,95E±4)	7,65E±3 (3,64E±3–1,50E±5)	0.33‡
CMV status of donor and recipient				0.28†
D-/R-	3	3	0	
D-/R‡	8	7	1	
D‡/R‡	10	9	1	
D‡/R-	25	17	8	
Route of (val)ganciclovir administration n (%)				0.72†
Oral	9 (19.6)	7.0 (25.0)	2.0 (20.0)	
Intravenously	9 (19.6)	9.0 (19.4)	0.0 (0.0)	
Consecutively IV-PO	28 (60.9)	20.0 (55.6)	8.0 (80.0)	
Duration of therapy (d); median (IQR)	107 (22–225)	89.0 (21.8–282.8)	143.0 (104.0–153.8)	0.91*
Leucocytes at baseline (10 ⁹ /mL)	5.6 (3.7–9.0)	4.8 (2.9–9.2)	7.4 (6.3–8.2)	0.25*
Lymphocytes at baseline (10 ⁹ /mL) median (IQR)	0.7 (0.4–1.4)	0.7 (0.4–1.3)	1.2 (0.5–2.6)	0.47‡
Neutrophils at baseline (10 ⁹ /mL) median (IQR)	3.3 (2.3–5.3)	3.1 (2.0–4.3)	4.5 (3.3–6.2)	0.12*

*Wilcoxon rank sum test.

†Fisher exact test.

‡t test ~ CMV infection: virus isolation or detection of viral proteins or nucleic acids in any body fluid or tissue specimen. CMV syndrome: CMV infection combined with fever ≥38°C for at least 2 d, new or increased malaise or new or increased fatigue, leukopenia or neutropenia, ≥5% atypical lymphocytes, thrombocytopenia, and elevation of aminotransferase level 2 times the upper limit of normal. CMV disease: CMV syndrome combined with end-organ disease (pneumonia, gastro-intestinal disease, hepatitis, retinitis, encephalitis, nephritis, cystitis, myocarditis, and pancreatitis).

The TDM characteristics are summarized in Table 2. A total of 28 patients (77.8%) reached their prespecified target trough level of 1–2 mg/L within 10.0 (3–20) days and 7

(70.0%) reached their target trough level of 2–4 mg/L within 9.0 (6.5–27.0) days (see Fig. 1). No statistically significant differences were observed (see Table 2).

TABLE 2. TDM Characteristics; Divided by Used Target Trough Level

	Target Trough Level 1-2 mg/L (n = 36)	Target Trough Level 2-4 mg/L (n = 10)	P*
	Median (IQR)	Median (IQR)	
All trough levels (mg/L)	1.7 (0.9–1.9)	1.5 (1.2–1.9)	0.74†
First trough level (mg/L)	1.6 (0.8–2.0)	1.1 (0.7–1.6)	0.76†
Number of trough levels obtained per patient	2.0 (2.0–4.0)	7.0 (3.3–8.8)	0.05‡
Time between start (v)GCV and reaching target trough of 1 mg/L (d)	10.0 (3.0–20.0)	6.0 (3.00–7.0)	0.75†
Time between start (v)GCV and reaching target trough of 2 mg/L (d)	12.0 (6.0–20.0)	9.0 (6.5–27.0)	0.95†

*Statistically significant, P < 0.05.

†t test

‡Wilcoxon rank sum test.

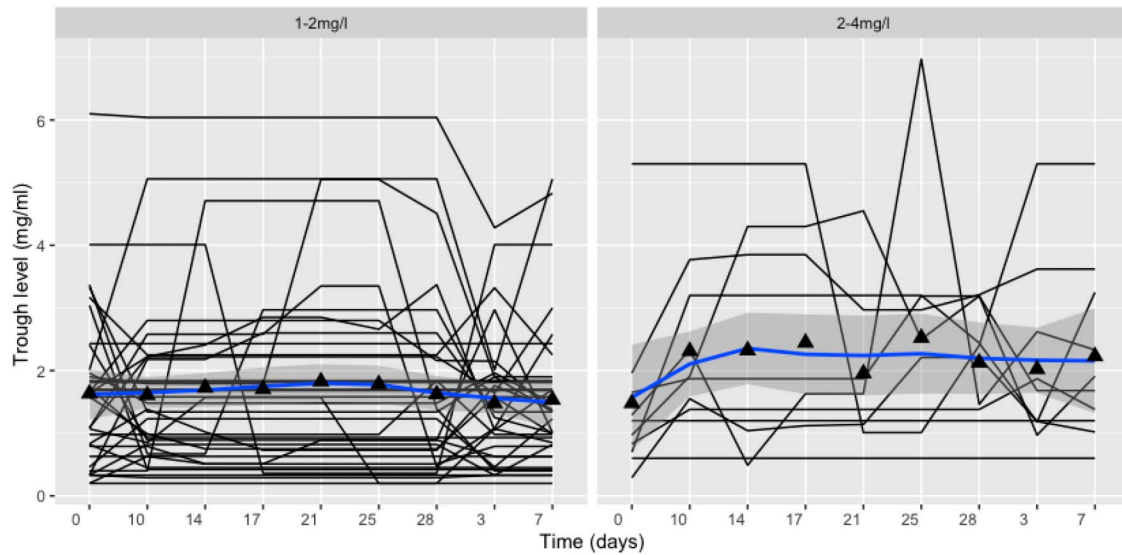


FIGURE 1. Trough levels over time (days), divided by target trough level used; blue line indicates median.

Primary Endpoint

The composite endpoint was reached by 23 of 36 patients, in whom a target trough level of 1–2 mg/L was used, and 6 of 10, in whom a level of 2–4 mg/L was used. No statistically significant differences were observed ($P = 1.0$).

Even when specified for patients who actually reached the target trough level of 2–4 mg/L (24 of 46), no statistically significant difference was found in reaching the composite endpoint ($P = 1.0$, see Table 3).

Secondary Endpoints

Using the GEE model, no statistically significant correlation between trough levels and the composite endpoint was found ($P = 0.75$). Using a GEE model, a correlation between trough levels and toxicity could be established for lymphopenia ($P = 0.01$), but not for nephrotoxicity ($P = 0.75$), anemia ($P = 0.66$), thrombocytopenia ($P = 0.69$), leukopenia ($P = 0.93$), and neutropenia ($P = 0.25$).

The occurrence of toxicity and its distribution in the groups with different target trough levels are summarized in Table 4. No statistically significant difference was found between the 2 groups.

There was no statistically significant difference in the viral decay time between the target trough level groups ($P = 0.93$). In addition, Cox regression showed no statistically

significant correlation between the target trough level and viral decay time, as shown in Figure 2 ($P = 0.36$, proportional hazards could be assumed according to Schoenfeld residuals ($P = 0.44$) and their independence of time).

Resistance analysis was performed in 14 patients, and resistant CMV strains were detected in 3 patients, all belonging to the 1–2 mg/L target trough level group ($P = 0.5$).

DISCUSSION

Our study could not establish a greater efficacy of (val)ganciclovir treatment of CMV infection in solid organ transplant recipients when a target trough level of 2–4 mg/L was used compared with the target trough levels of 1–2 mg/L. The initiation of foscarnet was noted more often in the 1–2 mg/L target trough level group, but this difference was not statistically significant. In addition, 3 versus 0 resistant strains of CMV were detected in the lower target trough level group, without any statistical significance. No correlation was found between repeated measures of ganciclovir trough levels and efficacy. A correlation between the occurrence of lymphopenia and trough level was demonstrated, but not with other forms of toxicity often attributed to (val)ganciclovir. Because of the low number of resistant strains detected, no statement can be made

TABLE 3. Composite Outcome and Its Components

	Occurrence n (%) Target Trough Level 1-2 mg/L N = 36	Occurrence n (%) Target Trough Level 2-4 mg/L N = 10	P*
Composite endpoint	23 (63.9)	6 (60.0)	1.0
>1 log ₁₀ rise in viral load	22 (61.1)	6 (60.0)	1.0
Initiation of foscarnet	8 (22.2)	0 (0)	0.17
Resistance analysis	10 (27.8)	4 (40)	0.46

* χ^2 test

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TABLE 4. Occurrence of Toxicity Specified by Used Target Trough Levels

	Occurrence n (%) Target Trough Level 1-2 mg/L	Occurrence n (%) Target Trough Level 2-4 mg/L	P*
Nephrotoxicity	9 (25.0)	5 (50.0)	0.71
Anemia	16 (61.5)	5 (50.0)	1
Thrombocytopenia	10 (27.8)	1 (10.0)	0.14
Leukopenia	13 (36.1)	0 (0.0)	0.06
Neutropenia	8 (22.2)	0 (0.0)	0.08
Lymphopenia	12 (33.3)	3 (30.0)	0.49

*Fisher exact test.

regarding the correlation between trough levels and the development of resistance.

In many care facilities, TDM of ganciclovir is routinely performed, although clinically established target trough levels are lacking. The in vitro established half-maximal inhibitory concentration (IC50) of ganciclovir is 0.1–2 mg/L.^{27,28} Some clinical studies support a trough level of 1 mg/L or higher, especially when used in a prophylactic setting. Piketty et al¹⁰ demonstrated a longer time to CMV retinitis recurrence in patients using ganciclovir as prophylaxis, with trough levels of 0.6 mg/L or higher. The area under the curve for ganciclovir of 50 mcg*h/mL was associated with an 8 times lower risk of developing viremia in contrast to the area under the curve of 25 mcg*h/L in another study,²⁹ which corresponds to a trough level of 1–2 mg/L. However, no clinical studies have been performed to establish ideal target trough levels for CMV treatment. In response to the manufacturer’s advice to double the dose for treatment of CMV as opposed to prophylaxis, a doubled target trough level was adopted in clinical practice, without any clinical validation. Our study highlights the need for further research because a higher target trough level may not lead to higher efficacy, but could lead to lymphopenia more frequently.

For ganciclovir to be biologically active, it must undergo several intracellular phosphorylation steps. In CMV-infected cells, ganciclovir is transformed to ganciclovir monophosphate by the viral protein kinase pUL97 and then to its active form, ganciclovir triphosphate, which is incorporated into viral DNA. Bilat et al showed great interindividual variability in intracellular concentrations of ganciclovir triphosphate and poor correlation with plasma concentrations of ganciclovir.¹³ Higher serum levels do not necessarily lead to higher intracellular concentrations of bioactive ganciclovir triphosphate, which may explain the lack of increase in the clinical efficacy of higher (target trough) levels of serum ganciclovir.

In accordance with other studies,^{11,16–20} our study did not establish a correlation between ganciclovir serum levels and efficacy. However, comparison of results is difficult because of the differences in patient populations and study methods. The association between ganciclovir exposure and leukopenia,^{2,29} anemia,^{12,18} thrombocytopenia,¹⁸ and nephrotoxicity² has been demonstrated in other studies; however, this could not be confirmed in our data. This could be explained by the fact that not all study groups used similar definitions of toxicity, the use of heterogeneous patient populations, and small sample size.

The difficulty in interpreting earlier studies lies in the fact that patients with various degrees of immunosuppression were included in the study. Viral clearance depends not only on adequate exposure to antivirals, but also on the function of the cellular immune system. Patients who underwent hematological stem cell transplantation had a higher degree of immunosuppression than patients who had undergone solid organ transplantation or chemotherapy. This is the strength of our study, which only included solid organ transplant recipients.

Our study had several limitations. The relatively small sample size makes it impossible to draw conclusions on the correlation between ganciclovir levels and toxicity and development of resistance because of the low occurrence of these outcomes. In addition, in accordance with other studies,^{2,12,30} a large proportion of patients did not reach the prespecified target trough level despite adequate dosing, which complicates the interpretation of the results. In particular, the comparison of the composite endpoint and Cox regression analysis viral decay time were affected by the lack of difference between the compared groups. It is not expected that the GEE analysis would be affected by this lack of difference because the prespecified target trough level was not incorporated in the model.

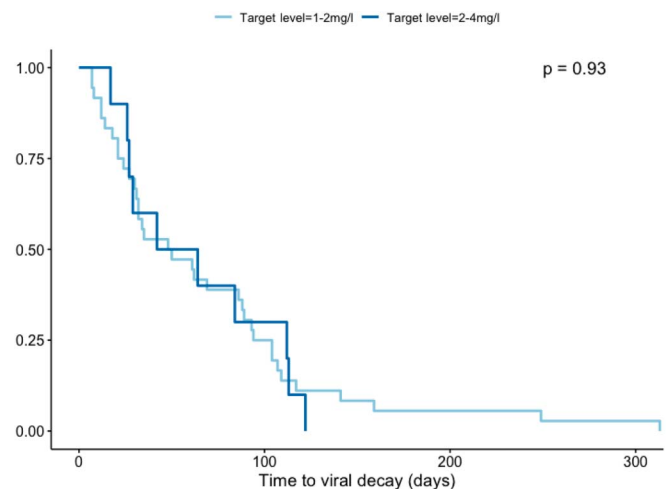


FIGURE 2. Viral decay time divided by used target trough level. Difference not statistically significant ($P = 0.93$, Kaplan–Meier curve).

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Patients in the 1–2 mg/L target group were treated for as long as 10 years ago. Although no differences in patient or treatment characteristics were noted between these groups, there might have been differences that were not accounted for in our analysis, which might have introduced bias in our study.

The exact types of immunosuppressive regimens and concomitant drugs (possibly causing blood dyscrasias) were not recorded in our database. Although the different types of organ transplants were evenly distributed between the 2 target level groups, bias could have been introduced because the levels of immunosuppression and use of other drugs can differ between these types of patients.

To make a definite decision on whether TDM of ganciclovir contributes to higher cure rates in the treatment of CMV infections in solid organ transplant patients and what target trough levels should be adopted, more research is needed. Randomized clinical trials are not suitable for this; however, a study design comparable to ours could be used. Collaboration between clinics is advised to be able to achieve a representative sample size and, subsequently, statistical power can be achieved. Further research should focus on the intracellular measurement of ganciclovir triphosphate, although this technique is not yet readily available and no established target trough levels exist for this application.

Because of its great interindividual variability, especially in patients with decreased kidney function, TDM could be beneficial for this patient category.² It may also be helpful in guiding clinicians in the decision to start second-line therapy (eg, foscarnet) when an otherwise unexplained lack of efficacy or toxicity arises. Second-line therapy has its disadvantages as well; therefore, although there is sparse evidence for clear cut-off values for efficacy or toxicity, very low or high levels of plasma ganciclovir could guide clinicians in this dilemma.

CONCLUSION

Our study could not establish a difference in clinical efficacy or toxicity in the use of a ganciclovir target trough level of 1–2 mg/L or 2–4 mg/L because of the lack of clinical differences between the compared groups. However, a correlation was found between repeated measurements of ganciclovir trough levels and lymphopenia, which warrants further research.

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