



A Systematic Review of the Clinical Pharmacokinetics, Pharmacodynamics and Toxicodynamics of Ganciclovir/Valganciclovir in Allogeneic Haematopoietic Stem Cell Transplant Patients

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Abstract

Background Ganciclovir (GCV) and valganciclovir (VGCV) are the first-line agents used to prevent and treat cytomegalovirus (CMV) infection in allogeneic haematopoietic stem cell transplant (alloHCT) patients.

Objective The aim of this work was to describe available data for the clinical pharmacokinetics, pharmacodynamics and toxicodynamics of GCV and VGCV and the potential of a therapeutic drug monitoring strategy to improve outcomes in the alloHCT population.

Methods We systematically reviewed the pharmacokinetics (dose-exposure), pharmacodynamics (exposure-efficacy) and toxicodynamics (exposure-toxicity) of GCV and VGCV in alloHCT patients with CMV infection. Studies including alloHCT patients treated for CMV infection reporting the pharmacokinetics, pharmacodynamics and toxicodynamics of GCV or VGCV were searched for using the PUBMED and EMBASE databases from 1946 to 2019. Only studies involving participants > 12 years of age and available in the English language were included.

Results A total of 179 patients were included in the 14 studies that met the inclusion criteria, of which 6 examined GCV pharmacokinetics only, while 8 also examined GCV pharmacodynamics and toxicodynamics. Reported pharmacokinetic parameters showed considerable interpatient variability and were different from other populations, such as solid organ transplant and human immunodeficiency virus-infected patients. Only one study found a correlation between neutropenia and elevated peak and trough GCV concentrations, with no other significant pharmacodynamic and toxicodynamic relationships identified. While therapeutic drug monitoring of GCV is performed in some institutions, no association between GCV therapeutic drug monitoring and clinical outcomes was identified.

Conclusion Further studies of the pharmacokinetics, pharmacodynamics and toxicodynamics of GCV/VGCV in alloHCT patients are required to identify a more robust therapeutic range and to subsequently quantify the potential value of therapeutic drug monitoring of GCV/VGCV in the alloHCT population.

1 Introduction

The management of haematological malignancies continues to be a significant global challenge, with many patients continuing to experience significant morbidity and mortality. Data from the UK from 2004 to 2011 indicates a prevalence

of 548.8 per 100,000 people for haematological neoplasms [1], which were ranked as the 8th leading cause of death and number of potential years of life lost in Australia in 2018 [2]. Allogeneic haematopoietic stem cell transplantation (alloHCT) is a potentially curative treatment modality for several haematological malignancies; however, with a 1-year treatment-related mortality rate of 15–20%, alloHCT itself is not without potential complications [3], including opportunistic infections, organ failure, graft-versus-host disease (GVHD), graft failure and others. Infection is a major cause of mortality in the first year post-alloHCT, accounting for approximately 15% of deaths in these patients [4].

Cytomegalovirus (CMV) is a major contributor to mortality in the alloHCT setting [5]. Depending on the CMV

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Key Points

Studies examining the pharmacokinetics of ganciclovir (GCV) and valganciclovir indicate a high degree of pharmacokinetic variability in the allogeneic haematopoietic stem cell transplant population.

There is currently limited evidence for any pharmacokinetic and pharmacodynamic/toxicodynamic relationships for GCV in this patient group.

Studies further examining the relationship of GCV pharmacokinetics, particularly area under the curve, to efficacy and toxicity endpoints are required to try and establish more robust pharmacokinetic/pharmacodynamic and pharmacokinetic/toxicodynamic indices to improve the optimal use of these agents.

serology status of donor and recipient and the conditioning regimen used, 30–80% of alloHCT patients will experience CMV infection or reactivation in the post-transplant period, requiring antiviral treatment. Approximately 5% of these patients progress to end-organ disease, such as CMV pneumonia, with a significant mortality rate of over 50% [5–7].

Pre-emptive antiviral CMV treatment is the current standard of care in most alloHCT centres [8, 9]. Intravenous ganciclovir (GCV) or the oral prodrug valganciclovir (VGCV) are the recommended first-line options for pre-emptive treatment of CMV infection/reactivation in alloHCT patients, while intravenous GCV is recommended for patients with proven CMV disease [10]. The main adverse effect of these agents is myelosuppression, manifesting as neutropenia but can also include thrombocytopenia and anaemia. Approximately 30% of alloHCT patients treated with GCV or VGCV develop neutropenia, which may in itself lead to other opportunistic infections [11, 12]. Given the importance of ensuring adequate exposure to avoid and treat CMV-associated organ damage, as well as the difficulty in distinguishing whether cytopenias are attributable to CMV or GCV toxicity versus other conditions such as pre-engraftment bone marrow aplasia or graft failure, therapeutic drug monitoring (TDM) may have a role for this drug with a narrow therapeutic index.

A recommended concentration range for GCV has been proposed based on measured concentrations in patients with normal renal function: peak concentration (C_{\max}) 4.75–9 mg/L, trough concentration (C_{\min}) 0.25–1.2 mg/L [13–15]. However, pharmacodynamic and toxicodynamic relationships have not been consistently identified [16]. There is no clear guidance on the current recommended dose of GCV and VGCV when used for pre-emptive CMV

therapy in the alloHCT population [17–21]. It is also uncertain if significant inter- and inpatient pharmacokinetic variability exists and whether this contributes to lack of efficacy, increased toxicity, or development of CMV resistance. This systematic review will examine the pharmacokinetics, pharmacodynamics and toxicodynamics of GCV and VGCV in alloHCT patients when used in pre-emptive CMV therapy or to treat CMV disease. We further aim to clarify how to optimise GCV use, including potential use of TDM, for more effective treatment with less toxicity in this population.

2 Methods

2.1 Data Sources and Strategy

This systematic review was conducted according to the PRISMA guidelines. The EMBASE and PUBMED databases were searched by two authors using the search terms ‘ganciclovir’, ‘valganciclovir’, ‘pharmacokinetics’, ‘drug monitoring’, ‘allogeneic haematopoietic stem cell transplantation’, ‘stem cell’, and ‘bone marrow transplantation’ (see electronic supplementary material). Publications were accepted from inception of the database until 30 April 2019, and publications were excluded if they were not available in the English language.

2.2 Study Eligibility and Selection Criteria

To be eligible for inclusion, studies had to include human subjects who had undergone alloHCT and (1) were aged ≥ 12 years; (2) described VGCV or GCV in the context of prophylaxis, pre-emptive treatment, or treatment of CMV; and (3) contained information on GCV concentration measured in plasma or serum.

Reviews, systematic reviews, and editorials were excluded. Given the significant heterogeneity in physiology and pharmacology in the paediatric literature, we concentrated on where the evidence is more concrete, i.e. in a population aged 12 years and over. Two reviewers (PRS and SS) were involved in the determination of study eligibility for the review. Initially, duplicate articles were identified and excluded. Articles were then screened based first on title and then on the abstract, progressing to full text of appropriate articles to further assess for eligibility. The reference lists of all full-text articles accessed was also searched to identify any other potential eligible studies not captured by the search strategy. Abstracts from conferences/scientific meetings were also included in the review if they met the above criteria.

2.3 Data Extraction

The following data were extracted into a predefined case report form from the eligible studies: study type, year of publication, age, sex, number of subjects, patient population, drug and dose, GCV assay used, whether serum or plasma were analysed, number of sampling time points, CMV diagnostic method, indication (prophylaxis, pre-emptive or treatment), pharmacokinetic parameters (C_{max} , C_{min} , exposure/area under the curve (AUC), half-life, clearance (CL), bio-availability), efficacy measurements (pharmacodynamics), toxicity measurements and whether these had any reported association with pharmacokinetic parameters (toxicodynamics). The coefficient of variation (%CV) for each of the pharmacokinetic parameters reported in the study was calculated from the mean and standard deviation. If the mean and standard deviation were not documented, they were calculated from the presented data if possible or if median and range were reported instead; the method documented by Hozo et al. was used to estimate the mean and standard deviations [22].

3 Results

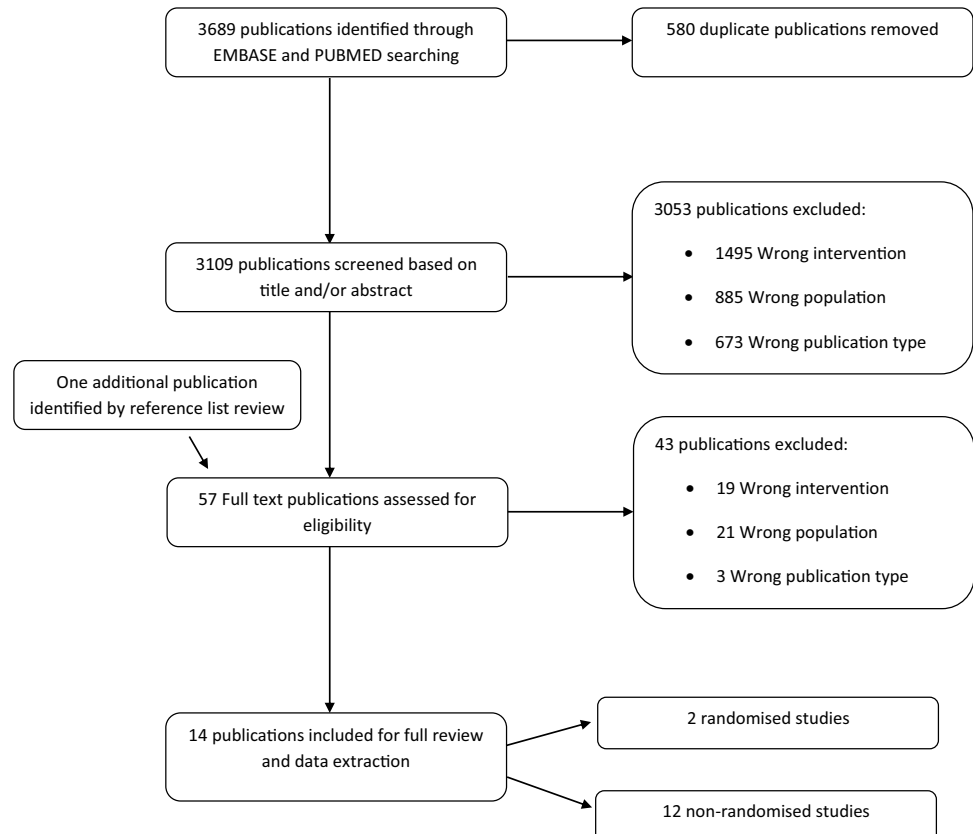
3.1 Studies Included in the Systematic Review

From the literature search, 3689 publications were identified—2877 from EMBASE and 812 from PUBMED. Of these, 580 duplicate publications were removed, leaving 3109 publications for screening based on their title and/or abstract, with 57 full-text publications further assessed. Further exclusions occurred, with one additional publication from reference lists included, providing 14 studies for full review and data extraction. Of these 14 studies, 6 described GCV pharmacokinetics only, while 8 reported GCV pharmacokinetics and pharmacodynamics or toxicodynamics (Fig. 1—PRISMA Flow Diagram).

3.2 Characteristics of Study Participants

A total of 179 subjects who had undergone alloHCT and received either intravenous GCV or oral VGCV were included in the review. The average age of participants in the studies ranged from 26 to 51 years and the proportion of females was 0–50% depending on the study (Table 1). The sample sizes ranged from 3 to 37 subjects. Patients were

Fig. 1 PRISMA Flow Diagram



grouped according to a measure of kidney function in two of the studies, and according to the presence of gastrointestinal (GI) GVHD in three of the studies. Characteristics of patients from the included studies are presented in Table 1, while the drug(s), dose(s), number of sampling points and reported pharmacokinetic parameters are shown in Table 2.

3.3 Ganciclovir Pharmacokinetics, Pharmacodynamics and Toxicodynamics in the Included Studies

In the six studies examining only the pharmacokinetics of GCV/VGCV, a range of intravenous GCV doses were used, with 5 mg/kg 12-hourly being the most frequent. Only one of the studies included oral VGCV, where 900 mg was administered as a single dose. When administered at a dose of 5 mg/kg (the standard dose when creatinine CL [CrCL] was > 70 mL/min), the mean AUC from time zero to 12 h (AUC_{12}) across the studies ranged from 47.7 to 52.8 $\mu\text{g}\cdot\text{h}/\text{mL}$. Four of the six studies reported peak GCV concentrations (C_{max}), with the mean values ranging from 5 to 13.3 $\mu\text{g}/\text{mL}$ [14, 23, 25, 26], while three of the studies reported trough GCV concentrations (C_{min}) with means ranging from 0.18 to 2.9 $\mu\text{g}/\text{mL}$ [14, 24, 25].

One study, an open-label, single-dose pharmacokinetic study, compared the pharmacokinetics of GCV after the administration of oral VGCV and intravenous GCV in alloHCT patients with no active CMV infection or disease and stable stage I–II acute or chronic GI GVHD [26]. The subjects received either a single dose of 900 mg oral VGCV or 5 mg/kg intravenous GCV, then, after a washout period, received the alternate drug. The mean (%CV) AUC_{12} values for a single dose of oral VGCV 900 mg and intravenous GCV were 49 (37) $\mu\text{g}\cdot\text{h}/\text{mL}$ and 51 (37) $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively, indicating no significant difference in this exposure measure between the two dosage forms. Mean (%CV) C_{max} was 6.7 (27) $\mu\text{g}/\text{mL}$ for oral VGCV, significantly lower than 13.3 (30) $\mu\text{g}/\text{mL}$ for intravenous GCV, while time to peak concentration was significantly lower for intravenous GCV, although these were both expected pharmacokinetic differences between the oral prodrug and intravenous GCV formulations. The authors of the study concluded that oral VGCV and intravenous GCV had similar pharmacokinetic parameters with the doses used, particularly AUC_{12} , which meant they would likely result in similar efficacy, although this needed to be confirmed by further randomised studies.

The study conducted by Asano-Mori et al. [25] evaluated whether halving the GCV dose for alloHCT patients with a CrCL of 50–70 mL/min, as recommended in the product information dosing guidelines, was appropriate. Twelve subjects were included in the study, with seven having CrCL > 70 mL/min, who were administered intravenous GCV

5 mg/kg (Group A), and five having CrCL of 50–70 mL/min, who were administered 2.5 mg/kg (Group B). This was the only study where CrCL was determined using a 24-h urine CrCL measurement. Where there was no significant difference in AUC_{12} between the two groups, the mean AUC_{12} in Group A was almost double that of Group B. This variance is likely due to the small sample size of the groups and the high CV% in group A. As a whole, the data do not support the authors' conclusions that the stipulated dose reduction is appropriate. Group A also contained a wide range of CrCL values (74.9–142 mL/min), which likely accounts for the high CV% value and may suggest dose banding is required at CrCL > 70 mL/min. It was also determined that the GCV concentration 4 h after the infusion had the strongest correlation with AUC, meaning it was likely this could be a critical point to be measured in a TDM strategy.

Eight of the included studies examined both GCV and VGCV pharmacokinetics, pharmacodynamics and toxicodynamics. Clinical outcomes differed between studies, but included mortality, time to 2-log reductions in CMV titres, observed clinical improvement, recurrence of CMV infection, development of CMV disease, time to negative CMV DNA polymerase chain reaction (PCR), neutropenia and thrombocytopenia.

Shepp et al. [27] undertook a study to evaluate the efficacy, safety, and pharmacokinetics of intravenous GCV in 10 alloHCT patients diagnosed with CMV pneumonitis. Neutropenia was defined as a decrease in absolute neutrophil count (ANC) to below $1 \times 10^9/\text{L}$ or a 50% reduction in ANC if the pretreatment ANC was lower than $1 \times 10^9/\text{L}$ for 2 consecutive days. This was the only GCV toxicity identified in the study and occurred in 40% of patients. The first five patients were treated with a dose of 5 mg/kg 8-hourly. Neutropenia was observed in three of the five patients administered at this level and was associated with a peak GCV concentration of > 12.8 $\mu\text{g}/\text{mL}$ and trough GCV concentration of > 2.6 $\mu\text{g}/\text{mL}$. Due to the high frequency of neutropenia at this dose level, the latter five patients in the study received a reduced dose of 2.5 mg/kg 8-hourly. This was the only study included in the review that demonstrated a pharmacodynamic or toxicodynamic relationship. However, the dosing used is significantly higher than all other studies included in this review, where doses no higher than 5 mg/kg 12-hourly were used and lower incidences of neutropenia were reported (11–35%) [28–31]. AUC was not reported in this study and could have been helpful in further elucidation of a pharmacokinetic/toxicodynamic index for GCV-associated neutropenia. This is because AUC has been the pharmacokinetic parameter associated with this toxicity in the solid organ transplant (SOT) population [35].

Lim et al. [31] carried out a prospective, open-label, randomised, phase I/II study to compare the bioavailability of oral VGCV and intravenous GCV for pre-emptive

Table 1 Characteristics of the included studies

Study	Year of publication	Population (n) ^a	Type	Age, years	Male (%)	GCV assay used	Indication
Pharmacokinetic studies							
Fletcher et al. [14]	1986	AlloHCT (5) [5 of 6]	Prospective cohort study	35	60	HPLC	Tx
Sommadossi et al. [15]	1988	AlloHCT (3) [3 of 21]	Prospective cohort study	31	77	HPLC and radioimmunoassay	Tx
Boeckh et al. [23]	1998	GI GVHD (2) No GI GVHD (5) [7 of 21]	Prospective cohort study	NS	NS	HPLC	Px
Shibata et al. [24]	2000	AlloHCT (5)	Retrospective cohort study	26	100	HPLC	Tx
Asano-Mori et al. [25]	2006	CrCL > 70 mL/min (7) CrCL 50–70 mL/min (5)	Prospective cohort study	50.5	75	HPLC	Pre
Winston et al. [26]	2006	GI GVHD (22)	Prospective randomized crossover clinical trial	45	73	HPLC/MS	NA ^b
Pharmacokinetic and pharmacodynamic/toxicodynamic studies							
Shepp et al. [27]	1985	AlloHCT (10)	Prospective cohort study	28	50	HPLC	Tx
Erice et al. [28]	1987	AlloHCT (9) [9 of 31]	Prospective cohort study	35	56	HPLC and ELISA	Tx
Winston et al. [29]	1988	Serum creatinine < 88.4 µmol/L (8) Serum creatinine 114.9–132.6 µmol/L (5) [13 of 36]	Prospective cohort study	34 (median)	75	HPLC	Tx
Einsele et al. [30]	2006	Without GI GVHD (22) With GI GVHD Grade 1–2 (5) With GI GVHD Grade 3 (1)	Prospective randomized crossover clinical trial	45	62	HPLC	Pre
Lim et al. [31]	2009	AlloHCT (18)	Prospective randomized phase I/II clinical trial	51 (median)	44	HPLC/MS	Pre
Awada [32]	2013	AlloHCT (12)	Prospective cohort study (conference abstract)	NS	NS	HPLC with UV	Tx
Gimenez et al. [33]	2014	AlloHCT (13)	Retrospective cohort study	50	46	HPLC with spectrofluorometric detection	Pre
Ritchie et al. [34]	2019	AlloHCT (37) [37 of 82]	Retrospective cohort study	54	50	NS	Pre and Tx

Data are expressed as mean unless otherwise indicated

AlloHCT allogeneic haematopoietic stem cell transplant, *CMV* cytomegalovirus, *CrCL* creatinine clearance, *ELISA* enzyme-linked immunosorbent assay, *GCV* ganciclovir, *GI GVHD* gastrointestinal graft-versus-host disease, *HPLC* high-performance liquid chromatography, *MS* mass spectrometry, *NA* not applicable, *NS* not stated, *Pre* pre-emptive treatment, *Px* prophylaxis, *Tx* treatment, *UV* ultraviolet

^aWhere (n of x) is noted in the population column, this refers to the number of AlloHCT patients within all subjects of the study

^bSingle-dose study in which patients did not have any active CMV infection

Table 2 GCV/VGCV dosing and pharmacokinetic parameters

Study	Population (n) ^a	Drug	Dose	Sampling timepoints (n)	C _{max} , µg/mL	C _{min} , µg/mL	AUC ₁₂ , µg·h/mL	t _{1/2} , h	Bioavailability, %
Pharmacokinetic studies									
Fletcher et al. [14]	AlloHCT (5) [5 of 6]	IV GCV	2.5mg/kg q8h	8	5.0 (15)	0.18 (155)	NS	2.6 (46)	NA
Sommadossi et al. [15]	AlloHCT (3) [3 of 21]	IV GCV	5mg/kg q12h	10	NS	NS	52.8 (38)	4.87 (18)	NA
Boeckh et al. [23]	GI GVHD (n = 2) No GI GVHD (n = 5) [7 of 21]	IV GCV	200 mg (single dose)	NS	7.0 (60) 6.0 (30)	NS NS	40.4 (88) 29.2 (48)	6.0 (3.3) 6.0 (25)	NA NA
Shibata et al. [24]	AlloHCT (5)	IV GCV	5 mg/kg q12h	1	NS	0.4	NS	NS	NA
Asano-Mori et al. [25]	CrCL > 70 mL/min (7) CrCL 50–70 mL/min (5)	IV GCV	5 mg/kg q24h 2.5 mg/kg q24h	8	10.8 (37) 5.9 (39)	1.1 (73) 0.59 (21)	47.7 (55) 25 (6.7)	4.61 (29) 6.36 (18)	NA NA
Winston et al. [26]	GI GVHD (22)	PO VGCV IV GCV	900 mg (single dose) 5 mg/kg (single dose)	15	6.7 (27) 13.3 (30)	NA	49 (37) 51.3 (37)	5.1 (28) 5.2 (29)	NS NA
Pharmacokinetic and pharmacodynamic/toxicodynamic studies									
Shepp et al. [27]	AlloHCT (10)	IV GCV	5 mg/kg q8h 2.5 mg/kg q8h	13	12.4 (44) 5.4 (13)	2.9 (75) 1.1 (27)	NS	3.6 (39)	NA
Erice et al. [28]	AlloHCT (9) [9 of 31]	IV GCV	2.5 mg/kg q8h	2	3.9 (23)	0.7 (100)	NS	NS	NA
Winston et al. [29]	Serum creatinine < 88.4 µmol/L (8) Serum creatinine 114.9–132.6 µmol/L (5) [13 of 36]	IV GCV	5 mg/kg q12h	2	11.5 (42) 11.6 (25)	1.4 (61) 1.6 (47)	NS	NS	NA
Einsle et al. [30]	Without GI GVHD (22) With GI GVHD Grade 1–2 (5) With GI GVHD Grade 3 (1)	PO VGCV IV GCV PO VGCV IV GCV PO VGCV IV GCV	PI PI PI PI PI PI	9	8.8 (27) 10.3 (21) 8.0 (41) 10.6 (31) 2.6 13.2	1.7 (55) 1.0 (65) 1.9 (41) 0.7 (51) 0.4 1.1	53.8 (33) 39.5 (35) 52.9 (41) 33.1 (39) 14.8 46.6	3.4 (24) 4.2 (26) 6.1 (31) 3.4 (22) 3.4 3.0	76.5 (24) NA 74.5 (19) NA NS NA
Lim et al. [31]	AlloHCT (18)	PO VGCV IV GCV	PI PI	4	NS NS	NS NS	36.9 (40) 27.9 (27)	NS NS	78.6 (32) NA
Awada [32]	AlloHCT (12)	IV GCV	5 mg/kg q12h	NS	9.4 (28)	NS	NS	6.4 (31)	NA
Gimenez et al. [33]	AlloHCT (13)	PO VGCV (3) IV GCV (10)	900 mg q12h 5 mg/kg q12h	1	NS NS	2.19 (108) 2.54 (82)	NS NS	NS NS	NS NA
Ritchie et al. [34]	AlloHCT (37) [37 of 82]	IV GCV	PI	2	6.0	1.9	NS	NS	NA

C_{max}, C_{min}, AUC₁₂, t_{1/2}, and bioavailability values are presented as mean (coefficient of variation), except for the study by Ritchie et al., which is presented as median. Where no coefficient of variation is listed, this was because a standard deviation or range was not reported in the study for this parameter

AlloHCT allogeneic haematopoietic stem cell transplant, AUC₁₂ area under the curve from time zero to 12 h, C_{max} maximum concentration, C_{min} minimum concentration, CrCl creatinine clearance, GCV ganciclovir, GI GVHD gastrointestinal graft-versus-host disease, IV intravenous, NA not applicable, NS not stated, PI product information, PO oral, q_{xh} every x hours, t_{1/2} half-life, VGCV valganciclovir

^aWhere (n of x) is noted in the population column, this refers to the number of AlloHCT patients within all subjects of the study

treatment of CMV in alloHCT patients. A total of 27 patients were included in the study, with 13 randomised to receive oral VGCV (Group A) and 14 randomised to receive intravenous GCV (Group B). Doses administered

were based on CrCL as per the product recommendations [36, 37]. There were no significant differences between the two treatment groups regarding efficacy or toxicity, and no association was found between AUC₁₂ and efficacy

or safety. While the mean AUC_{12} of GCV was higher in patients administered oral VGCV (36.9 $\mu\text{g}\cdot\text{h}/\text{mL}$), the difference was not significant compared with those administered intravenous GCV (27.9 $\mu\text{g}\cdot\text{h}/\text{mL}$).

A prospective, randomised, multicentre, crossover, open-label clinical trial was conducted by Einsele et al. [30] to provide pharmacokinetic data on oral VGCV compared with intravenous GCV in the pre-emptive treatment setting of CMV viremia in 48 alloHCT patients. Patients received either oral VGCV for 7 days then intravenous GCV for 7 days or vice versa. Doses were adjusted for CrCL as per the product information. Efficacy of treatment was measured as the time to negative CMV PCR in blood and the incidence of CMV disease up to 84 days post VGCV or GCV treatment. Safety was measured as the incidence of serious adverse events, CMV-related mortality, overall mortality, and neutropenia determined by numbers of patients with $\text{ANC} < 1 \times 10^9/\text{L}$ and $< 0.5 \times 10^9/\text{L}$ at days 8, 15 and 22. Thirty-seven of forty-five (82.2%) patients achieved negative CMV DNA, while only two patients (4.2%) developed CMV disease. The overall mortality was 12.5% (none related to CMV) and neutropenia occurred in 27% of patients. Twenty-eight of 48 patients in the study were included in the final pharmacokinetic analysis and were classified as either having no GI GVHD ($n = 22$), grade 1 or 2 GI GVHD ($n = 5$) or grade 3 GI GVHD ($n = 1$). Unexpectedly, mean AUC_{12} was significantly higher for oral VGCV compared with intravenous GCV in patients without GI GVHD and grade I–II GI GVHD. The one patient with grade III GI GVHD showed poor absorption of oral VGCV and a significantly reduced AUC_{12} . The study found no association between AUC_{12} , C_{max} or C_{min} and either efficacy or safety measures.

A 10-year retrospective analysis by Ritchie et al. [34] aimed to determine whether GCV TDM was associated with efficacy or safety during intravenous GCV treatment. Eighty-two patients were included in the analysis, with 37 of these patients being alloHCT patients. GCV TDM was performed randomly at the discretion of the treating physician, and performed a median of 7 days into GCV therapy. Only serum GCV peak and trough concentrations were measured, with a recommended target peak concentration of 3–12 $\mu\text{g}/\text{mL}$ and target trough concentration of 1–3 $\mu\text{g}/\text{mL}$. No significant association was found between GCV peak and trough concentrations and either safety or efficacy endpoints, leading the authors to state the utility of GCV TDM may be of limited value, except in certain patient populations or those with unpredictable pharmacokinetics. The study did however state that large interindividual variability in GCV peak (median 6.0 $\mu\text{g}/\text{mL}$, interquartile range 4.7–9.5 $\mu\text{g}/\text{mL}$) and trough concentrations (median 1.9 $\mu\text{g}/\text{mL}$, interquartile range 1.0–3.0 $\mu\text{g}/\text{mL}$) was demonstrated.

4 Discussion

4.1 Pharmacokinetic Variability

Based on previous studies, mean AUC CV% values for GCV after administration of intravenous GCV and oral VGCV range from between 17 and 20% for healthy subjects, 12.9% and 31% for HIV patients, and 6% and 53% for SOT patients [38]. From the studies evaluated in this review, %CV values for AUC_{12} in alloHCT patients ranged from 6.7 to 88%. The lowest %CV value of 6.7% for AUC_{12} was reported in a population sample from the study performed by Asano-Mori et al., which included five patients administered a dose of 2.5 mg/kg, with an estimated CrCL of 50–70 mL/min [25]. This low value was likely due to the narrow range of renal function for this patient group and the small sample size, likely resulting in underrepresentation of the true extent of the %CV. This was also the only study where CrCL was estimated using a 24-h urine creatinine measurement, potentially resulting in more accurate estimation of renal function. The highest %CV value of 88% occurred in a sample of only two patients and was likely a result of the small sample size [23]. When compared with the mean CV% ranges in the other mentioned populations, there appears to be more pharmacokinetic variability in the alloHCT patient group, although this is difficult to prove statistically due to the different study methods, dosing regimens, and sample sizes utilized. When the highest and lowest AUC CV% values are removed for the alloHCT studies for the reasons as described previously, the CV% values range from 27 to 55%. Considering the narrow therapeutic index of GCV [38], we would argue these values constitute considerable pharmacokinetic variability of GCV after the administration of intravenous GCV or oral VGCV.

The source of this pharmacokinetic variability could be due to many factors. It has been extensively demonstrated that GCV CL is proportional to glomerular filtration, with the percentage of renal CL quoted as 91% [14, 39]. However, renal function estimation in the alloHCT population is difficult and it has been shown that common methods used to estimate CrCL in alloHCT patients tend to be inaccurate, especially when GFR is < 90 mL/min [40, 41]. Doses of oral VGCV and intravenous GCV are adjusted according to glomerular filtration rate, in line with the current product information [36, 37]. Inaccurate estimation of renal function, as may occur in the alloHCT population, could therefore result in a high variability in GCV concentrations when the product dosage recommendations are followed, as was the case in most studies in this review. Sepsis and multiorgan dysfunction syndromes are also common in the alloHCT population [42, 43]. For certain antimicrobials, sepsis will

affect the volume of distribution (Vd), which then influences C_{max} . Altered renal function can also occur as a result of sepsis, which affects CL and is often not accurately reflected by serum creatinine in the acute setting [44]. This is particularly the case for hydrophilic drugs such as GCV [16]. AlloHCT patients being treated with GCV or VGCV may have sepsis syndromes due to CMV infection itself or other concurrent viral, bacterial or fungal infections, resulting in altered Vd and CL in these patients, which could have contributed to the pharmacokinetic variability of GCV in many of the analysed studies. Significant inpatient variability of GCV half-life, CL and Vd was specifically mentioned in one of the publications [32].

Another potential source of this variability may be due to the toxic effects of conditioning chemotherapy regimens on renal tubular function in alloHCT patients, which may also occur due to hepato-renal syndrome in the context of veno-occlusive disease of the liver [45]. Tubular secretion has been shown to be an important process in GCV CL, and impaired tubular secretion may not necessarily be reflected in the calculated CrCL [14, 46]. Thus, a significant reduction in GCV CL may occur in the alloHCT population depending on the extent of renal tubular damage. This may not be accounted for by renal function estimates that are based on serum creatinine and could lead to doses being not appropriately adjusted when product dosing recommendations are followed. Importantly, the study by Asano-Mori et al. reported a comparatively much lower %CV value for AUC_{12} and was also the only study to measure CrCL using 24-h urine CrCL quantification [25]. This may indicate that more accurate measurements of renal function to guide GCV dosing could result in less pharmacokinetic variability.

In addition to the observed significant interpatient pharmacokinetic variability, there also appear to be noticeable differences between GCV pharmacokinetics in the alloHCT group and other populations, such as those who have undergone SOT or are infected with human immunodeficiency virus (HIV). Several studies reported a higher AUC_{12} and longer half-life in alloHCT patients treated with either GCV or VGCV compared with other populations previously studied, with the suggested reason being alterations in renal tubular secretion as discussed previously [23, 26, 30]. GCV bioavailability after administration of VGCV was also reported to be higher in the alloHCT population, with gut toxicity from conditioning chemotherapy regimens being theorised to be responsible for this [28, 30]. This pharmacokinetic variability lends credence to the idea that further study of GCV pharmacokinetics in the alloHCT population alone may be worthwhile to determine whether different dosing guidelines or a TDM strategy may be beneficial.

4.2 Pharmacodynamics and Toxicodynamics

In the eight studies that included pharmacokinetic, pharmacodynamic and toxicodynamic analysis of GCV and VGCV, an association between elevated GCV peak and trough concentrations and neutropenia was found in only one study [27], while no other relationships were identified; however, the small sample sizes of the studies may explain this finding. The relationship between GCV/VGCV concentrations and efficacy or toxicity has not been well characterized in any population [16].

Activation to GCV triphosphate is required for GCV to exert both its antiviral and myelosuppressive effect achieved through inhibition of DNA replication [47]. In vitro data show the GCV concentration required to inhibit human CMV growth by 50% (EC_{50}) ranges from 0.02 to 3.5 $\mu\text{g/mL}$ [36]. The clinical myelotoxic effects observed with GCV result from the increased sensitivity of bone marrow cells when compared with other cell types, to the toxic effects of GCV [47]. This has been shown by in vitro studies, with the 50% inhibitory concentration (IC_{50}) of GCV against bone-marrow cell cultures ranging from 0.68 to 3 $\mu\text{g/mL}$ [36, 48, 49]. This is in comparison with other non-haematopoietic human cell lines, where much higher mean IC_{50} values of 25–90 $\mu\text{g/mL}$ are reported [50, 51]. The reasons for this are thought to be differences in uptake, phosphorylation, and potency of DNA polymerase inhibition of GCV between cell types [47]. While in vitro data indicate dose-dependent myelotoxicity of GCV [48, 49], duration of exposure has also been shown to be important [52]. A study by Janoly-Dumenil et al. demonstrated reducing IC_{50} values on B lymphoblastoid cell lines, with increased time of GCV exposure up to 14 days. This is relevant to the clinical setting as most courses of GCV/VGCV for alloHCT patients are of at least 14 days' duration, and exposure to the reported IC_{50} value of 3 $\mu\text{g/mL}$ at this timepoint is likely with the currently used dosage regimens [52]. The study also showed that higher GCV concentrations caused no more inhibition of cell growth than lower concentrations with a short duration of exposure. This may indicate prolonged GCV exposure to enable intracellular accumulation is likely required for toxicity to be realised. The findings from this study led the same authors to conduct an in silico investigation that suggested intermittent higher dose, shorter duration of GCV therapy to treat CMV infection to reduce myelotoxicity [53]. Most mean C_{max} values from the examined studies exceed the EC_{50} and IC_{50} concentrations, while many of the mean C_{min} values are within the reported concentration ranges. While there is currently no established relationship between clinical response and in vitro sensitivity of CMV to GCV, the similarity in EC_{50} and IC_{50} values likely results in a narrow therapeutic index of GCV when being used for CMV

treatment [38]. This is particularly the case with longer treatment courses that are often administered in the alloHCT setting. This means it may not be possible to effectively treat CMV with GCV/VGCV without causing haematological toxicity in many clinical scenarios with currently recommended dosage regimens.

A number of studies have suggested that AUC correlates with the efficacy of GCV and VGCV in the prevention and treatment of CMV infections [14, 54–56]. As efficacy and toxicity are dependent on the combination of concentration as well as time-dependent effects, the most robust pharmacokinetic measure of total exposure, i.e. the AUC, may have the best correlation with efficacy and toxicity. Furthermore, single C_{\min} or C_{\max} concentrations have limited reliability in indicating the total extent of cumulative exposure over the entirety of a treatment course. Significant effects of sample timing in relation to the attainment of steady-state concentration also contribute to the variability. Of the studies included in this review that examined clinical endpoints, only two reported AUC_t . These were a crossover study and a randomised phase I/II study, both of which had the primary aim of comparing the GCV exposure of oral VGCV with intravenous GCV in the alloHCT population [30, 31]. The two studies agreed that oral VGCV did result in significantly higher GCV AUC_{12} than intravenous GCV when product dosing recommendations were followed; however, the crossover design of one of the studies and the small sample size ($n = 18$) of the other study may explain the lack of association with clinical efficacy. A comparison of oral GCV with oral VGCV in 372 SOT patients showed an association between GCV exposure and suppression of viremia, with an AUC_{24} of ≥ 45 mg \times h/L associated with a lower risk of CMV viremia [35]. This seems to indicate a degree of relationship between GCV exposure and efficacy. However, smaller studies have not shown this relationship, meaning suitably large sample sizes are likely required to show this correlation [13, 57, 58].

The study conducted by Shepp et al. [27] found an association between peak and trough GCV concentrations and the development of neutropenia; however, this relationship was not shown in any of the other analysed studies. The haematological toxicity of GCV has been shown to be dose- and time-dependent in the *in vitro* setting [48, 52], thus it would be expected that the magnitude and duration of GCV exposure would play a role in the risk of developing neutropenia in patients undergoing treatment with GCV. In the SOT population, one study found a weak association between GCV exposure and haematological toxicity [35], while other studies have not shown an association [54, 57]. A reason for the lack of a relationship between pharmacokinetic parameters determined from GCV plasma or serum concentrations and neutropenia could be a result of this adverse effect being dependent on intracellular

GCV-triphosphate concentrations, as demonstrated by Billat et al. [59]. While intracellular GCV-triphosphate concentrations likely have some dependence on extracellular GCV concentrations, this is difficult to characterise due to membrane transporters that can be affected by genetic variation, such as multidrug resistance-associated protein 4 (MRP4), which is involved in GCV transfer across cell membranes [60]. There are also numerous factors other than GCV for neutropenia post-alloHCT, such as viral infections, including CMV itself, use of other myelotoxic agents, graft source, and conditioning chemotherapy regimen intensity, among others [61]. These confounding factors present significant difficulty in the determination of a pharmacokinetic–toxicodynamic relationship for GCV-induced neutropenia.

Three studies have examined risk factors for GCV-associated neutropenia in the alloHCT population [45, 62, 63]. A cohort study of 278 consecutive patients found bilirubin > 6 mg/dL during the first 20 days of alloHCT, serum creatinine > 176.8 μ mol/L after day 21, and low marrow cellularity between days 21 and 28 post-transplant were significant risk factors for GCV-related neutropenia [45]. The increased bilirubin was likely an indication of hepatic veno-occlusive disease, which often leads to renal tubular damage associated with hepatorenal syndrome and reduced GCV CL, as has been previously mentioned [14, 45, 46]. A smaller study of 47 patients showed a CrCL < 50 mL/min, absence of corticosteroid therapy, and transplantation with bone marrow stem cells rather than cord blood stem cells were risk factors [62]. A retrospective cohort study of 160 patients by Venton et al. demonstrated high CMV viral load, ANC $< 3 \times 10^9$ /L at the time of GCV treatment initiation and serum creatinine > 176.8 μ mol/L after day 21 post-transplant to be significantly associated with GCV-induced neutropenia [63]. The association of high viral load with neutropenia may be explained by the direct suppressive effects of CMV on haematopoiesis that have been demonstrated *in vitro* and would be expected to be increased with a higher viral burden [64]. Furthermore, increased viral load has been associated with longer time to CMV CL and may therefore result in increased duration of GCV treatment courses, potentially further increasing the risk of neutropenia [65]. Low bone marrow cellularity and reduced initial ANC, identified as risk factors in two of the studies, likely show suboptimal engraftment and therefore a lower tolerance for haematological toxicity. All three studies identified reduced renal function as a risk factor for GCV-induced neutropenia. Because GCV CL is proportional to renal function and therefore renal impairment results in increased AUC [39], a relationship between the amount of GCV exposure and the development of neutropenia would be favoured. Furthermore, doses in the studies were as per product recommendations and thus would have been adjusted for renal function, yet impaired renal function was still identified as a risk factor

for neutropenia. This may indicate that the GCV/VGCV dose adjustments suggested in the product information for reduced CrCL may not be appropriate for the alloHCT population. As discussed previously, there appears to be considerable pharmacokinetic variability of GCV between patient populations, however dosing guidelines across all these patient groups are very similar.

Risk factors for GCV-induced thrombocytopenia were investigated in a retrospective single-centre study by Matsumoto et al. in 185 adult patients [66]. The number of participants who had undergone alloHCT was not specified, however 94 patients had haematological malignancies. Administration of cancer chemotherapy within 14 days before or during GCV therapy, GCV dose >12 mg/kg/day and CrCL <20 mL/min estimated using the Cockcroft–Gault formula were identified as risk factors for GCV-induced thrombocytopenia [66]. Like GCV-induced neutropenia, the latter two risk factors identified appear to indicate increased GCV exposure is also a factor in causing thrombocytopenia and overall bone marrow toxicity. Pharmacokinetic/toxicodynamic relationships for the less common adverse effects of GCV/VGCV, such as hepatotoxicity and nephrotoxicity, have not been investigated.

4.3 Therapeutic Drug Monitoring

Only one study was included in the review that examined the potential for TDM of GCV/VGCV to improve patient outcomes, and found no association between the use of TDM and toxicity or efficacy endpoints [34]. However, only 37 of the 82 patients included in this study had undergone alloHCT and there was no subanalysis of this group. TDM of GCV is a potentially attractive strategy to help improve CMV treatment outcomes in the alloHCT patient population due to the high level of PK variability and significant consequences of therapeutic failure and toxicity; however, this approach is limited by the lack of a clearly demonstrated relationship between GCV concentrations and pharmacological effects, particularly neutropenia [16]. While some institutions do perform routine TDM of GCV in alloHCT patients, this is not yet a universal standard [67]. Before routine GCV TDM can be recommended, pharmacokinetic/pharmacodynamic and pharmacokinetic/toxicodynamic indices need to be identified so a more robust therapeutic range or target can be determined. From the studies in other populations, AUC appears to be the most promising pharmacokinetic parameter for this. Even though AUC may be the optimal pharmacokinetic parameter to summarise the effect of concentration as well as time of exposure, measuring this in the clinical setting can be difficult, with multiple blood samples required. A concentration measurement at a single timepoint enabling accurate estimation of AUC

would be ideal. A study of oral GCV in lung transplant recipients showed a significant correlation of C_{\max} and C_{\min} with AUC, with a standard dose of 1 g three times daily [68]. However, considering the different dosage intervals employed, depending on renal function estimates, and the frequent changes that can occur in Vd and CL in alloHCT patients, single C_{\max} or C_{\min} concentrations may not always accurately reflect AUC. One study in this review found the concentration at 4 h after intravenous GCV administration had the best correlation with AUC, proposing this timepoint could be utilised for TDM [25]. Another potential approach as part of a TDM strategy to enable more accurate AUC estimation from a single timepoint could be the development and use of a priori probability Bayesian methods for GCV [69]; however, before a defined TDM strategy can be developed, larger studies examining the correlation of AUC with clinical endpoints in the alloHCT population are needed.

5 Conclusion

Current studies examining the pharmacokinetics of GCV and VGCV indicate a high degree of pharmacokinetic variability in the alloHCT population. Furthermore GCV/VGCV pharmacokinetics in this patient group seem to vary from other populations, such as SOT and HIV-infected patients. Evidence is currently lacking for the correlation of GCV/VGCV pharmacokinetics with efficacy or toxicity endpoints, while therapeutic concentration targets are not well established in the alloHCT population. Considering these findings, studies further examining the pharmacokinetics, particularly AUC, pharmacodynamics and toxicodynamics of GCV/VGCV in alloHCT patients are needed to clarify the optimal use of these agents to improve treatment effectiveness with reduced toxicity. The development of dosing algorithms based on more accurate measures of renal function, and examination of alternative dosing strategies such as higher dose, shorter duration therapy is also warranted. More robust linkage between GCV pharmacokinetics and pharmacodynamics/toxicodynamics is required before the utility of a TDM strategy can be established.

Declarations

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Authors' contributions PS, SS, MW and JR conceived the present idea. PS and SS undertook the database search, determined study eligibility for the review and extracted the relevant data from the studies for review. PS, SS, SP, MW, DY, UH and JR evaluated and interpreted the included studies. PR wrote the first draft of the manuscript and critical revision was undertaken by SS, SP, MW, DY, UH and JR. All authors read and approved the final version of the manuscript.


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