Received: 8 March 2024 | Revised: 3 May 2024 | Accepted: 13 May 2024

DOI: 10.1111/bcp.16138

THEMED ISSUE ARTICLE

Challenges for the improvement of valganciclovir prophylaxis in solid organ transplantation and the possible role of therapeutic drug monitoring in adults

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Funding information
For this manuscript no specific grant from any funding agency in the public, commercial, or not-for-profit sectors was received

Cytomegalovirus (CMV) infection frequently occurs after solid organ transplantation and is associated with an increased morbidity and mortality. Fortunately, the development of valganciclovir prophylaxis has lowered the incidence of CMV infection and its complications in immunosuppressed solid organ transplant recipients. However, breakthrough infections during valganciclovir prophylaxis and late CMV infection after cessation of valganciclovir prophylaxis still occur with the current prophylactic strategy. Additionally, valganciclovir resistance has emerged among CMV strains, which complicates the treatment of CMV infections. Furthermore, the use of valganciclovir is associated with myelotoxicity, which can lead to the premature withdrawal of prophylaxis. It is important to address these current issues in order to improve the standard care after solid organ transplantation. This paper will therefore discuss the clinical practice of valganciclovir prophylaxis, elaborate on its issues and suggest how to improve the current prophylactic strategy with a possible role for therapeutic drug monitoring.

KEYWORDS
ganciclovir, solid organ transplantation, therapeutic drug monitoring, valganciclovir

1 | INTRODUCTION

Transplantation is a life-saving procedure for the treatment of terminal cardiac, liver and lung failure. It is also the preferred treatment of end-stage renal disease, with superior clinical and patient-reported outcomes compared to dialysis.[1]

A major and frequent complication of solid organ transplantation (SOT) is cytomegalovirus (CMV) infection. CMV is a herpesvirus that is present in the majority of the adult population.[2] In immunocompetent individuals, the course of a de novo CMV-infection is mainly asymptomatic and reactivation rarely occurs. However, in immunosuppressed SOT recipients, CMV can cause major problems both by the reactivation of latent virus in previously infected, seropositive recipients and by the de novo infection of CMV-seronegative patients (i.e. *primo* CMV infection).[2] Symptomatic CMV infection can be categorized as CMV syndrome, which is associated with symptoms such as malaise and fever, and CMV disease which is comprised of organ-specific disease such as pneumonia, chorioretinitis and colitis.[2] CMV disease can have a fatal outcome.[2] Before the development of effective antiviral medication with anti-CMV efficacy, the prevalence of CMV was high: the incidence of CMV disease has been reported in up to 20% of liver transplant recipients.[3] Fortunately, the development of medication such as acyclovir and ganciclovir have made it possible to adequately prevent and treat CMV disease.[4] Today, valganciclovir, a valine ester prodrug of ganciclovir with superior oral bioavailability, is the most used agent for CMV prophylaxis and treatment in SOT.[5]

Although the incorporation of ganciclovir and valganciclovir into standard care after SOT substantially improved outcomes, it has not

eradicated all CMV-associated complications. CMV infection still occurs frequently,[6] either through breakthrough infections during prophylaxis or late CMV infection after cessation of prophylaxis. Another complication is ganciclovir-resistance among CMV, which occurs in up to 25% of CMV breakthrough infections,[7] and is associated with increased mortality and morbidity.[8] Importantly, ganciclovir exposure is also associated with myelotoxic effects,[9] which can necessitate dose reductions or even early cessation of prophylaxis with the risk of subsequent CMV infection in up to 15%.[10]

The aforementioned problems have instigated researchers and pharmaceutical companies to develop new anti-CMV drugs with the aim of finding agents with superior efficacy and tolerability compared to valganciclovir. Recently, such a new anti-CMV drug, letermovir, was approved and registered for use in kidney transplantation.[11] Although these new drugs have great potential, they also come at greater costs. For instance, the average price of letermovir in the Netherlands is €327/day,[12] which is >40 times higher than the price of generic valganciclovir (€7.93/day).[13] Therefore, it might be worthwhile to improve valganciclovir prophylaxis in order to limit ganciclovir toxicity, premature discontinuation, therapy failure and ganciclovir resistance.

This paper will briefly review the current clinical practice of valganciclovir prophylaxis for CMV infection prevention after SOT in adults, and identify the issues that are associated with its current use. The possible role of personalized medicine and therapeutic drug monitoring (TDM) to address these issues will be discussed and suggestions will be made on how to fill the knowledge gaps regarding TDM of valganciclovir.

2 | CLINICAL PRACTICE—DEVELOPMENT OF A PROPHYLACTIC STRATEGY

This section will cover the development of valganciclovir as a prophylactic agent to prevent CMV infection. It will briefly discuss the efficacy of ganciclovir and valganciclovir and review some of the available scientific evidence that supports the current consensus with regard to prophylaxis duration and valganciclovir dosing in adults. However, it is not an in-depth analysis of all available scientific evidence of this matter. The interested reader is referred to several recent systematic reviews and meta-analyses.[14–16]

2.1 | Ganciclovir—a potent inhibitor of CMV

Ganciclovir was developed in the 1980s as the first effective treatment of CMV disease.[17] It suppresses the replication of viral DNA by selectively inhibiting viral DNA polymerase.[18] The use of ganciclovir as a CMV prophylactic in SOT was established in the 1990's and thereafter.

In the first studies, ganciclovir was administered intravenously,[19,20] which limited the duration of prophylaxis. A short course of intravenous ganciclovir significantly lowered the incidence of symptomatic CMV for seropositive heart transplant recipients,[19] but a prolonged prophylaxis with intravenous ganciclovir was more effective.[20] However, due to late CMV infections, this significant early difference diminished during study follow-up.[20] Furthermore, the use of intravenous catheters limited its practical applicability and led to several complications.[20]

Subsequently, the use of oral ganciclovir was studied, which enabled a longer duration of prophylaxis. In liver-transplant recipients, 3 months of oral ganciclovir prophylaxis was safe and effective.[3] Other studies also showed that oral ganciclovir was superior to oral acyclovir for CMV-prevention after kidney transplantation,[21] kidney, heart or liver transplantation,[22] and liver transplantation.[23]

2.2 | Valganciclovir—a ganciclovir prodrug with superior bioavailability

Although oral ganciclovir was an effective CMV prophylactic, ganciclovir was known for its low oral bioavailability of around 6%.[24] Therefore, a valine-ester prodrug of ganciclovir, valganciclovir, was developed. Valganciclovir has a short absorption time and is rapidly metabolized to ganciclovir.[25] This leads to a 10-fold higher oral bioavailability of valganciclovir compared to ganciclovir.[26]

Oral valganciclovir was shown to lead to significantly less CMV infection during prophylactic treatment compared to oral ganciclovir, but late-onset CMV infection occurred frequently after cessation of prophylaxis.[27] Valganciclovir was also shown to be more effective than a short course of intravenous ganciclovir,[28] and equally effective as 3 months of intravenous ganciclovir in seronegative recipients.[29]

2.3 | Prophylaxis duration—extending prophylaxis for patients at risk

From the efficacy studies described above, it was shown that valganciclovir did not adequately prevent late CMV infections. Retrospective studies found that patients after lymphocyte-depleting agents such as alemtuzumab and seronegative recipients of a seropositive donor organ (D+R−) were more at risk for late CMV infection.[30] Extending the duration of prophylaxis was suggested to decrease late CMV infection in D+R− patients.[31] A large, randomized, double-blind trial confirmed that 200 days of valganciclovir prophylaxis led to significantly less CMV-infections during the first year after transplantation compared to 100 days of valganciclovir prophylaxis for D+R− kidney transplant patients.[32] In contrast, 3 months of prophylaxis seemed appropriate after lymphocyte depletion[33] and recipients with CMV seropositive status.[34] For lung transplant recipients, a further extension of valganciclovir prophylaxis up to 12 months post-transplantation was shown to be safe and effective.[35]

In accordance with these findings, the international guideline of the Transplantation Society state that a duration of prophylaxis of 6 months is preferable for all D+R− kidney transplant recipients,

while for liver, heart and pancreas D+R− recipients a duration of 3 months may suffice.[5] Contrarily, longer duration of prophylaxis may be considered for lung transplant recipients.[5]

2.4 | Prophylactic dose—current advice

Valganciclovir 900 mg once daily is the currently recommended dose for CMV prophylaxis, both by the international guideline of the Transplantation Society as by the manufacturer.[5,36] This dose was shown to have a comparable drug exposure as ganciclovir intravenously.[24,37] The efficacy of this dose of valganciclovir was confirmed in the aforementioned studies.[27–29]

Valganciclovir 450 mg once daily has also been studied as a standard dose.[38–42] In seropositive kidney transplant recipients, a reduced dose of 450 mg valganciclovir/day was found to have a comparable efficacy and superior safety compared to 900 mg/day after 6 months of prophylaxis[38] and 3 months of prophylaxis[39] despite a high number of patients receiving lymphocyte-depleting induction therapy. In seronegative, high-risk kidney transplant recipients, the results are conflicting. One retrospective study found comparable efficacy and less leukopenia after 6 months of 450 mg,[40] but another retrospective study found an increased risk of breakthrough-infection.[42] Studies of low-dose valganciclovir may have been confounded by differences in the kidney function of study participants. As discussed below, the kidney function is an important factor that influences ganciclovir exposure. The lack of measurements of ganciclovir exposure in these studies therefore limit the generalizability of any conclusions regarding the safety and efficacy of low-dose valganciclovir. This, together with the paucity of the available evidence, were reason to recommend against the routine use of low-dose valganciclovir in the international guideline of the Transplantation Society.[5]

2.5 | Dialysis and kidney function-adjusted dosing

Ganciclovir is primarily cleared by the kidneys.[43] Oral administration of valganciclovir in the standard dose of 900 mg valganciclovir once daily will lead to higher ganciclovir concentrations in patients with reduced kidney function,[44] which can lead to overdosing and severe myelotoxicity.[45] Therefore, valganciclovir is dosed based on the kidney function.[36] The current prophylactic dosing advice is 900 mg of valganciclovir once daily for patients with a creatinine clearance (CrCl) >60 mL/min, 450 mg once daily with CrCl 40–59 mL/min, 450 once every 2 days with CrCl 25–39 mL/min and 450 mg twice a week with CrCl 10–24 mL/min.[36] Haemodialysis is estimated to remove half of the amount of ganciclovir from the body.[43] Therefore, valganciclovir should be dosed after haemodialysis. The recommended dose of valganciclovir is 100 mg after each haemodialysis session.[5] However, recent reports showed that higher doses might also be safe and effective: 450 mg 3 times a week after haemodialysis leads to comparable CMV-infection and myelotoxicity as kidney function-adapted dosing in patients not on haemodialysis.[46] Furthermore, compared to dosing 450 mg every other day, 450 mg 3 times a week after dialysis led to higher cell counts and comparable CMV-infection rates.[47] Lastly, a recent study reported on the use of oral valganciclovir for patients on continuous veno-venous haemodialysis and concluded that daily dosing of 450 mg valganciclovir was safe and led to adequate ganciclovir predose concentrations in this specific patient population.[48]

3 | CURRENT ISSUES—TARGETS FOR IMPROVEMENT

3.1 | Ganciclovir-related toxicity—myelotoxic effects

The use of valganciclovir is associated with several side effects. The most common side effects of valganciclovir, are myelotoxicity (neutropenia, anaemia and leukopenia) and diarrhoea.[36] Although these adverse reactions also commonly occur with other medication used in SOT, it was shown that myelotoxicity occurs significantly more often with valganciclovir prophylaxis.[49] The myelotoxic effects that are observed with valganciclovir are caused by active ganciclovir. Ganciclovir interferes with leukocyte proliferation by inhibiting DNA synthesis.[50] Importantly, myelotoxicity has been recorded as a major reason for early valganciclovir prophylaxis discontinuation,[51] and subsequent late CMV-infection.[52] Risk factors for ganciclovir-related toxicity are high (val)ganciclovir doses and a decreased kidney function.[53]

3.2 | Late CMV-infection—risk factors for postprophylactic failure

CMV infections commonly occur after cessation of valganciclovir prophylaxis and both tissue-invasive, late CMV infection and CMV viraemia are associated with an increased risk of an allograft loss.[54,55] There are factors associated with a late CMV infection or a CMV infection in general: the importance of the donor-recipient serostatus is reflected in the indication for and duration of prophylaxis. D+R− donor–recipient combinations have the highest risk of postprophylactic failure. Other, potential risk factors for the development of late CMV disease have been identified through retrospective studies in kidney transplantation. Patient-related risk factors include patient comorbidity,[54] susceptibility to bacterial and fungal infections[54] and older patient age.[56] These risk factors can probably be interpreted as an indicator of the frail patient. Immune-suppression related risk factors include recent rejection,[57,58] the use of lymphocyte depleting antibodies and higher mean tacrolimus predose concentrations.[59] These risk factors probably increase the risk of late CMV infection by inhibiting the immune system to mount an adequate immune response against CMV. Lastly, there are risk factors, such as a lower estimated kidney function,[59,60] a higher bodyweight[59] and delayed

graft function (defined by the necessity of dialysis the first week after kidney transplantation).[58] It could be argued that these risk factors are related to lower ganciclovir exposure: a patient with a higher bodyweight can have higher distribution volumes and may need higher dosages for the same ganciclovir exposure. However, contrary to dosing with ganciclovir i.v., valganciclovir is not adjusted for bodyweight. Furthermore, lower kidney function or dialysis could lead to dose reductions that are too strict for the actual kidney function. Because these studies did not measure ganciclovir levels, the association between these risk factors, low ganciclovir exposure and the increased occurrence of CMV infection remains speculative.

3.3 | Ganciclovir-resistant CMV—important cause of breakthrough infections

CMV resistance to ganciclovir soon emerged after ganciclovir became available to treat severe CMV infection in AIDS patients.[61] With the use of ganciclovir in SOT, ganciclovir-resistant CMV disease also occurred in solid organ recipients.[62] Different mutations can underlie ganciclovir resistance, but the most common are mutations in the UL97 and UL54 genes.[63] UL97 is a viral protein kinase that initiates the phosphorylation of ganciclovir, which is an imperative process for ganciclovir to inhibit CMV replication.[63] UL54 is the viral DNA polymerase that incorporates the phosphorylated ganciclovir in the viral DNA, thus inhibiting further DNA replication. Mutations in both genes can results in ganciclovir resistance, but UL54 mutations can also result in cross-resistance against other anti-CMV therapies, which can complicate the treatment of resistant CMV disease.[63]

Ganciclovir resistance is an important cause of CMV breakthrough infections. The incidence of ganciclovir-resistant CMV differs based on the transplanted organ and the CMV monitoring protocol. The incidence ranges from 2.2% (in kidney transplant recipients who were regularly monitored for any CMV viraemia),[64] up to 22% in patients that were selected because of high CMV titres under (val) ganciclovir therapy.[65]

Ganciclovir-resistant CMV disease has a significant effect on the outcome of treatment. It is associated with a higher mortality and a decreased kidney function.[66] Risk factors for the development of ganciclovir-resistant CMV are D+R− transplantation and prolonged exposure to ganciclovir.[65,66] Ganciclovir-resistant CMV disease has also been observed after subtherapeutic exposure to ganciclovir.[67] These risk factors reflect potential targets for the improvement of valganciclovir prophylaxis with the aim of reducing ganciclovir-resistant CMV-infection.

4 | THERAPEUTIC DRUG MONITORING

The appraisal of the current clinical practice and the associated issues of valganciclovir prophylaxis after SOT in adults has identified multiple targets for the improvement of the current prophylactic strategy. Because ganciclovir exposure is related to both its efficacy, toxicity and the development of viral drug resistance, monitoring of ganciclovir exposure through TDM is suggested. Not all drugs are good candidates for TDM. TDM can be considered for drugs that meet certain criteria that were summarized by Buclin *et al.*[68] Valganciclovir meets some of these criteria: the treatment duration of valganciclovir is sufficient for TDM to be feasible, and there is no direct measurement of its clinical effect. Other criteria that a drug should have to qualify for TDM are: a significant interindividual variability in exposure; a consistent concentration exposure relationship; and a narrow therapeutic index. These will be discussed here. Furthermore, the role of population pharmacokinetic models in TDM will be reviewed.

4.1 | Interindividual differences—variability in drug exposure

The pharmacokinetics of valganciclovir and ganciclovir exhibit substantial interindividual variability.[69] This is reflected by the large variability in ganciclovir exposure that is recorded after oral valganciclovir in pharmacokinetic studies, with reported areas under the curve (AUCs) ranging between 10 and 200 μg h/mL.[70] Part, but not all, of this interindividual variability can be explained by variables such as the kidney function, which strongly affects ganciclovir clearance, and bodyweight, which has an effect on both the ganciclovir clearance and the distribution volume of ganciclovir.[70] To illustrate, the variability in clearance in these studies was around 33% despite the covariate effects of CrCl.[71–73] Thus, ganciclovir exposure can differ between individuals despite correcting for the kidney function. This is also shown by the pharmacokinetic study of Caldes *et al*. who reported AUCs between 20 and 85 μg h/mL despite renal function-adjusted dosing.[74]

Ganciclovir serum/plasma concentration measurements are readily available in most transplant centres. A suggested approach to deal with the persistent interindividual differences in ganciclovir exposure despite kidney-function adjusted dosing, is by concentration-guided dose adjustments in individual patients.[69] However, this approach requires stable within-subject variability over time. Within-subject variability was shown to be negligible for intravenous ganciclovir pharmacokinetics,[75] intra- and interday differences were <15%,[73] and intra- and interassay variation was <10%.[71] Furthermore, this approach requires clear cut-off values that define the target for adequate ganciclovir exposure.

4.2 | Exposure targets—what to aim for?

With respect to ganciclovir toxicity, AUCs were shown to only correlate weakly to myelotoxicity by Wiltshire *et al*.: median incidences of 40% of leukopenia up to 4 months post-transplant were predicted for patients with an AUC of 34 μg h/mL and 50% with an AUC of 62 μg h/mL.[76] Welker *et al*. found a trend of developing leukopenia or

lymphopenia under higher ganciclovir exposure, but the number of events and the range of ganciclovir exposure were limited, therefore the findings were not statistically significant.[77] Padullés *et al*. reported a significantly higher incidence of anaemia in patients with AUC values >50 μg h/mL, compared to patients below this value (51.9 *vs*. 26.6%, $P = .010$).[78] However, it is unclear for what period patients were overexposed. Most studies have found that predose concentrations and peak concentrations are not significantly correlated with toxicity during the treatment of CMV infection.[77,79,80] In a single report, therapeutic predose concentrations were found to correlate with lymphopenia.[81] Importantly, ganciclovir predose concentrations were recently shown to correlate with severe leukocytopenia after valganciclovir prophylaxis in lung transplantation, with a cut-off value of 0.87 μg/mL for predicting severe leukocytopenia.[82] In summary, ganciclovir exposure might be related to myelotoxicity, but the available evidence is scarce. The association of single concentration measurements, either predose or peak, to myelotoxicity is even weaker.

Ganciclovir exposure is positively related to its efficacy. A ganciclovir AUC of 40–50 μg h/mL was found to effectively suppress CMV viraemia during prophylaxis and until 1 month after cessation of prophylaxis.[76] With a target AUC of 40–50 or 40–60 μg h/mL, breakthrough CMV infections could also be effectively prevented or reduced.[77,78] In most publications therefore, an AUC of 40–60 μg h/mL during prophylaxis is defined as on target exposure. A single concentration is easier to obtain than an AUC. Therefore, prophylactic targets based on predose concentrations or peak concentrations would be more useful in daily practice. Unfortunately, the available clinical data do not support the use of either a predose concentration target nor a peak concentration target, for neither was correlated with the effectiveness of valganciclovir prophylaxis[80] or treatment of CMV infection.

Ganciclovir-resistant CMV has developed after sub-therapeutic exposure to ganciclovir, both after oral valganciclovir prophylaxis[67] and ganciclovir therapy for CMV infection.[83] Although there is no direct evidence of causality in these cases, subtherapeutic exposure is a well-known risk factor for the development of drug-resistance.[67,84] Furthermore, some authors have reported success in the prevention of ganciclovir resistance by aiming for ganciclovir predose concentrations of 0.35–0.7 μg/mL with TDM.[85]

4.3 | Population pharmacokinetics—model-informed TDM

Population pharmacokinetic models can be used for model-informed precision dosing (MIPD), which takes into account the interindividual variability between patients and thereby optimizes ganciclovir exposure. Multiple population pharmacokinetic models of ganciclovir and valganciclovir were published in the last years. The probability of target attainment after standard, therapeutic valganciclovir dosing and the effect of several covariates in different populations was estimated with these models.[86] Therapeutic target attainment was defined as an AUC between 80 and 120 μg h/mL. Standard, therapeutic valganciclovir dosing in adult patients was shown to lead frequent overexposure (defined as an AUC above 120 μg h/mL).[86] Extrapolating the outcomes of these simulations to the prophylactic doses suggests frequent overexposure (>60 μg h/mL) after valganciclovir prophylaxis too. MIPD that includes actual kidney function, bodyweight and current ganciclovir exposure, was suggested to improve target attainment.[86] To our knowledge, only 1 study compared the efficacy of such a model-based dosing algorithm to the standard kidney function-adjusted dosing for valganciclovir prophylaxis in SOT.[78] This study, by Padullés *et al*., included 53 heart, kidney and liver transplant recipients who received oral valganciclovir or intravenous ganciclovir for either CMV prophylaxis or therapy for CMV infection.[78] Patients were randomized to receive the standard, kidney-function adjusted (val)ganciclovir dose ($n = 27$) or to receive an initial dose that was calculated with a population pharmacokinetic model ($n = 26$). In the latter group, subsequent doses were corrected based on MIPD. The main study outcome was the percentage of patients that reached target AUCs (defined as 40–50 μg h/mL). A significantly larger proportion of patients that were dosed with the prediction model were on target (88.6% of model-dosed patients *vs*. 22.2% of standard dosed patients, $P < .001$).[78] The time to reach target AUC was also significantly shorter in the model-dosed patients (15.8 ± 2.3 days *vs*. 55.9 ± 8.2 days, $P < .001$). Furthermore, the incidence of late-onset CMV infection was significantly lower after model-informed dosing.[78]

The measurement of a full AUC for ganciclovir requires frequent sampling. This method is inconvenient for the patient, costly and burdens the hospital facility. This limits the use of AUCs for the evaluation of MIPD and for the implementation of TDM. In the study of Padullés *et al*., AUCs were obtained with an optimal sparse sampling schedule that was previously developed by the same research group.[87] With population pharmacokinetic models, an optimal sparse sampling strategy can be developed that estimate accurate AUCs with as few samples as possible. The optimal sparse sampling strategy used by Padullés *et al*., was developed using simulations from a previously developed population pharmacokinetic model for different sampling schedules and kidney functions.[87] Twenty sampling schedules were evaluated and the optimal sparse sampling strategy to estimate the $AUC_{0-24\ h}$ included 3 sample timed at 0.5–1.5, 4–5 and 6–8 h after (val)ganciclovir administration.[87] Importantly, this optimal sparse sampling strategy was not externally validated. Furthermore, it was developed to estimate the AUCs of therapeutic (val)ganciclovir and was not validated for the estimation of an AUC for valganciclovir prophylaxis. Chen *et al*. also published a population pharmacokinetic approach for valganciclovir prophylaxis.[73] With the development of a population pharmacokinetic model in a training dataset, the use individual population pharmacokinetic parameters in a validation dataset were estimated with a Bayesian approach. These parameters were used to estimate the $AUC_{0-24\ h}$ for different sampling schedules. A comparison of the estimated AUCs to the measured AUCs in this validation dataset, showed that the optimal sparse sampling strategy to obtain AUCs during valganciclovir prophylaxis included measurements at 0, 2 and 4 h.[73] Although Chen *et al*. did validate their model, it was a small ($n = 30$) validation cohort that was generated with a random data

split. The population consisted of all Chinese, kidney transplant recipients. Their model and limited sampling schedule should therefore be validated in a larger population of different origin too.

5 | DISCUSSION—SUGGESTIONS FOR FUTURE DIRECTIONS

Valganciclovir is an effective prophylactic to prevent CMV infection in SOT. However, the prophylactic use of valganciclovir has limitations. Although new agents such as letermovir are very welcome additions to the anti-CMV antiviral repertoire, it is doubtful that these will solve all valganciclovir-related issues, such as the occurrence of viral resistance, which has already been observed after secondary letermovir prophylaxis.[88] Furthermore, the costs of letermovir are substantially higher than the costs of valganciclovir. The results from published studies suggest that there might be a role for personalized medicine strategies and TDM of valganciclovir prophylaxis to reduce (severe) myelotoxicity, improve the efficacy and reduce the occurrence of viral resistance. It is of paramount importance that new studies are undertaken to fill the hiatuses regarding the knowledge of risk factors of adverse events and the dose–exposure–response relationship of (val) ganciclovir.

A reduction in severe myelotoxicity could be accomplished by personalized dose adjustments, as is suggested by the studies that found comparable efficacy and reduced toxicity after 450 mg of valganciclovir for some groups of SOT recipients.[38–41] Population studies are needed to find additional factors for the identification of patients who can be safely treated with lower dosages of valganciclovir prophylaxis, and randomized trials as exemplified by the study of Halim *et al.* should be conducted to test the safety and efficacy of these personalized dosing regimens.[38] Importantly, these studies must include ganciclovir concentration measurements in order to associate reduced dosing with actual lower ganciclovir exposure and evaluate if this will lead to better safety and comparable efficacy outcomes. This will also help to (re)define exposure targets for valganciclovir prophylaxis.

Late and breakthrough (resistant) CMV infections might be prevented by optimizing drug exposure. Model-informed precision dosing has the potential to reduce ganciclovir underexposure as was shown by Padullés *et al.*,[78] but the effect of model-informed precision dosing on clinical endpoints such as late and breakthrough infections should still be determined.

Another possible improvement to reduce late CMV infections, could be to extend the duration of valganciclovir prophylaxis for at-risk patients. In our centre, patients who are treated with lymphocyte depleting antibodies receive valganciclovir prophylaxis as long as their T lymphocytes are $<200 \times 10^6$/L, independent of the time after depletion therapy.[89] Other risk factors for late CMV infection are known, and it would be interesting to study if these patients at risk might also benefit from longer valganciclovir prophylaxis. Implementation of TDM for patients under long-lasting prophylaxis might help to avoid overexposure and myelotoxicity, which could improve drug adherence. Additionally, it could also help to avoid underexposure and drug resistance during these periods of prolonged prophylaxis. Considering the bad correlation between predose concentrations and efficacy outcomes, AUCs should be the target of TDM. For implementation of these targets in clinical practice, it is important to validate optimal sampling strategies such as reported by Padullés *et al.* and Chen *et al.*[73,87]

Considering the implementation of TDM for valganciclovir, it is clear that valganciclovir indeed has a high interindividual variability, but that there is not enough high-level evidence that defines the exact concentration–exposure relationship and supports the use of the current AUC targets. Together with the absence of evidence that TDM effectively improves the outcomes of prophylaxis, it cannot be advised that TDM should be implemented for valganciclovir at this time. However, it is the authors' opinion that the suggested trials and the regular measurements of ganciclovir concentrations after valganciclovir prophylaxis in daily practice should be undertaken, not despite, but because of these limitations. Prospective trials and retrospective analysis of drug exposure after valganciclovir and clinical outcomes are needed to provide more data about the valganciclovir dose–exposure–response relationship and personalization strategies. In addition, the authors would like to stress the importance of collaborative research consortia to effectively tackle these issues: National and international collaborations would enable a fast recruitment of patients, which provides researchers with the large cohorts that are necessary to externally validate optimal sampling schedules, model-based dosing and criteria for prophylaxis personalization. It could also help to coordinate the evaluation of TDM strategies. Ideally, these research endeavours should be coordinated by the different transplant organizations, which would allow for research prioritization.

6 | CONCLUSION

Valganciclovir is an effective prophylactic for the prevention of CMV infections in SOT, but myelotoxicity, late CMV infection and viral resistance are important clinical issues associated with its use.

Personalized medicine and TDM have the potential to optimize the use of valganciclovir prophylaxis, and should therefore be more extensively studied, ideally through coordinated research endeavours and international research collaborations.

ACKNOWLEDGEMENTS

Not applicable.

CONFLICT OF INTEREST STATEMENT

D.H. received lecture and consulting fees from Astellas Pharma, Astra Zeneca, Chiesi Pharma, Medincell, Novartis Pharma, Sangamo Therapeutics, and Vifor Pharma. He received grant support from Astellas Pharma, Bristol-Myers Squibb and Chiesi Pharma (paid to his institution). D.H. does not have employment or stock ownership at any of these companies, nor does he have patents or patent applications. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

There is no dataset associated with this publication.

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How to cite this article: van Vugt LK, Hesselink DA, de Winter BCM. Challenges for the improvement of valganciclovir prophylaxis in solid organ transplantation and the possible role of therapeutic drug monitoring in adults. *Br J Clin Pharmacol*. 2025;91(6):1551-1559. doi:10.1111/bcp.16138