

Management of CMV Infection and Disease in Transplant Patients

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KEY WORDS

■ HAEMATOPOIETIC STEM CELL TRANSPLANT ■ BONE MARROW TRANSPLANT ■ SOLID ORGAN TRANSPLANT ■ CYTOMEGALOVIRUS ■ GUIDELINES ■ RECOMMENDATIONS ■ VALGANCICLOVIR

SUMMARY

The *International Herpes Management Forum* (IHMF®) has published guidelines for the diagnosis and management of cytomegalovirus (CMV) infection and disease in solid organ (SOT) and haematopoietic stem cell transplant (HSCT) recipients. These recommendations have been updated to include, among others: (1) use of whole blood for the polymerase chain reaction (PCR) diagnosis of CMV infection; (2) CMV load measurements for prognostication and for monitoring response to anti-CMV therapy; (3) valganciclovir prophylaxis in CMV donor-positive/recipient-negative (D+/R-) SOT patients for prevention of CMV disease; (4) oral ganciclovir prophylaxis, in preference to aciclovir, to reduce incidence of CMV disease in SOT patients; (5) pre-emptive therapy with oral ganciclovir to reduce incidence of CMV disease and viraemia in liver transplant patients; (6) valganciclovir prophylaxis, in preference to high-dose oral aciclovir, to prevent CMV infection in allogeneic HSCT patients; and (7) foscarnet as an alternative to intravenous ganciclovir for pre-emptive treatment of CMV infection in allogeneic HSCT patients. New developments in the field requiring further research were highlighted, including: optimal frequency of CMV monitoring in CMV D+/R- SOT patients; optimal duration of prophylaxis for the prevention of late CMV disease; need for an acceptable viral threshold for initiation of pre-emptive therapy; and assessment of the clinical efficacy of valganciclovir for the treatment of CMV disease and as pre-emptive therapy in SOT and HSCT patients. This article presents supporting evidence for these recommendations and statements.

Introduction

IN NOVEMBER 2001, the *International Herpes Management Forum* (IHMF®) published its recommendations for the management of cytomegalovirus (CMV) infection and disease in transplant patients.¹ In response to the research needs identified by the IHMF® at that time, there have been significant new developments in the diagnosis of CMV, which have improved our understanding of the dynamics of CMV infection after transplantation. Furthermore, there have been numerous clinical trials involving prophylactic and pre-emptive antiviral therapies for the prevention of CMV disease, and these have contributed significant knowledge to the way in which CMV should be managed. Hence, there was a need to revisit, update and supplement the 2001 recommendations pertaining to the diagnosis and management of CMV in transplant patients.

This article represents a summary of the presentations and discussions held at the 11th Annual Meeting of the IHMF®, which took place in The Netherlands, 27–29 February 2004. At the meeting, experts in CMV proposed draft recommendations based

on new data, and these were discussed and ratified by the delegates. The recommendations formulated by the IHMF® and outlined here cover the management of CMV after solid organ transplantation (SOT) and haematopoietic stem cell transplantation (HSCT). Throughout this document, the term 'haematopoietic stem cell transplant' is used in preference to 'bone marrow transplant' in order to describe more accurately the current state of transplantation, which could involve harvesting donor cells from the peripheral blood, umbilical cord blood or bone marrow.

Cytomegalovirus infection and disease in neonates, pregnant women and HIV-infected individuals are outside the scope of this article but will be addressed by the IHMF® in the future. This publication features only the *new* guidelines for the management of CMV disease in transplant patients; a complete listing of all the recommendations published by the IHMF® is available from www.ihmf.org.

CMV: an Ominous Pathogen

Human CMV, a member of the *Betaherpesvirinae*, has the ability to establish lifelong persistent and latent infection following primary exposure.² Under certain conditions, CMV can reactivate, resulting in asymptomatic viral shedding or development of disease. CMV evades the host's defence function through several mechanisms, but ultimately, in the immunocompetent individual, the infection is held in check by the host's immune response.³ Hence, CMV disease is generally restricted to the immunocompromised or immunologically immature host. In transplant patients, infection with CMV from the donor organ or the reactivation of CMV in the recipient can lead to disease development.¹

Cytomegalovirus disease is considered the single most important infectious complication after SOT.⁴ CMV is a major cause of morbidity and can present as lung, liver, gastrointestinal, renal or retinal disease in SOT patients.⁵ CMV is also a major complication of haematopoietic stem cell transplantation (HSCT),⁶ with incidences of 15–60% and 20–35%, respectively, of CMV infection and disease.⁷ In HSCT patients, the most frequent clinical manifestations of CMV are pneumonitis, fever and gastrointestinal disease⁸ (Table 1), although hepatitis, retinitis, myelosuppression and encephalitis can also occur.⁹

In addition to the direct end-organ diseases, CMV is also associated with acute graft rejection; chronic graft rejection including bronchiolitis obliterans (in lung recipients), vanishing bile duct syndrome (in liver recipients) and accelerated transplant vasculopathy (in heart recipients). It is also associated with bacterial and fungal superinfection; CMV could interact with other viruses resulting in accelerated hepatitis C virus pathogenesis and increased incidence of Epstein–Barr virus-associated post-transplant lymphoproliferative disease. Collectively, all of these conditions are termed the 'indirect effects' of CMV.¹⁰

RECOMMENDATIONS AND STATEMENTS

Diagnosis and monitoring of CMV infection

- CMV load measurements can be used to monitor response to therapy and to predict the time required to reduce CMV load to undetectable levels (category 1 statement)
- Although detection of CMV by polymerase chain reaction (PCR) in many compartments of blood (plasma, leucocytes, etc.) can provide prognostic information, CMV DNA levels in whole blood are significantly higher than those present in plasma, so whole blood should be the sample of choice (category 1 recommendation)
- Owing to the rapid dynamics of CMV, a randomized, controlled trial is needed to determine the optimum sampling frequency for quantitative measures of viral load (research need recommendation)
- An international quantitation standard distributed by an external quality control organization is required to compare studies using different PCR-based systems and to facilitate patient management at multiple care centres (research need recommendation)

Treatment of established CMV disease

- Valganciclovir can be utilized to achieve clinically effective doses of ganciclovir for the treatment of established disease. Clinical trials are required to ensure adequate therapeutic levels are achieved in patients with poor absorption, e.g. in patients with gastrointestinal graft-versus-host disease (research need recommendation)
- Further studies are required to define how control of CMV replication is affected by the lower valganciclovir doses needed in patients with renal dysfunction (research need recommendation)

Prevention of CMV in solid organ transplant patients

Prophylactic therapy:

- For CMV D+/R- SOT patients who have received 5–10 days of intravenous (IV) ganciclovir prophylaxis, oral ganciclovir prophylaxis could be offered, in preference to oral aciclovir, to reduce the incidence of CMV disease (category 1 statement)
- Oral ganciclovir prophylaxis is as effective as IV ganciclovir for the prevention of CMV disease in CMV D+/R- liver transplant patients who had received IV ganciclovir during the initial 14 days after transplantation (category 1 statement)
- Valganciclovir prophylaxis for 100 days is as effective as oral ganciclovir for 100 days for the prevention of CMV disease in CMV D+/R- SOT patients but patients should be monitored for neutropenia (category 1 statement and recommendation)
- Compared with oral ganciclovir, valganciclovir prophylaxis is associated with a significantly lower incidence of CMV viraemia during prophylaxis and a later onset of CMV viraemia after completion of prophylaxis (category 1 statement)
- To reduce the incidence of CMV disease, CMV-seropositive liver transplant patients could be offered oral ganciclovir prophylaxis in preference to oral aciclovir (category 1 recommendation)
- CMV D+/R- SOT patients remain at risk of CMV disease after completing 100 days of antiviral prophylaxis, and so monitoring of CMV in blood is highly desirable after cessation of prophylaxis (category 2 recommendation)

- The optimal duration of antiviral prophylaxis for the prevention of late-onset CMV disease needs to be assessed in a controlled clinical trial, together with monitoring of drug resistance development (research need recommendation)

Pre-emptive therapy:

- Pre-emptive therapy with oral ganciclovir (1 g three times daily for 8 weeks), upon the detection of CMV DNA, reduces the incidence of CMV disease and viraemia in liver transplant patients. However, the compound is not as effective for patients with high viral loads at the time of initiation of pre-emptive therapy as it is for those with lower viral loads (category 1 statement)
- The clinical efficacy of valganciclovir for the treatment of CMV infection in SOT patients needs to be evaluated in a prospective, randomized clinical trial (research need recommendation)

Prevention of CMV in haematopoietic stem cell transplant patients

Prophylactic therapy:

- After engraftment, valaciclovir prophylaxis is as effective as IV ganciclovir in reducing CMV infection and disease, but valaciclovir is associated with more therapeutic intervention with alternative antiviral regimens because of possible or proven CMV infection or disease (category 1 statement)
- In allogeneic haematopoietic stem cell transplant (HSCT) patients, valaciclovir prophylaxis should be offered, in preference to high-dose oral aciclovir, to reduce CMV infection (category 1 recommendation)

Pre-emptive therapy:

- Pre-emptive therapy with foscarnet is as effective as IV ganciclovir for the prevention of CMV disease in allogeneic HSCT patients, but patients should be monitored for electrolyte abnormalities (category 1 statement and recommendation)
- The clinical efficacy of valganciclovir for the treatment of CMV infection in HSCT patients needs to be evaluated in a prospective, randomized clinical trial (research need recommendation)

Note: Where these recommendations allude to the use of oral ganciclovir, clinicians may wish to use valganciclovir as the preferred formulation for anti-CMV prophylaxis.

RECOMMENDATION AND STATEMENT CATEGORIES

The IHMF® publishes management recommendations and statements under four categories, which are:

Category 1

Consistent evidence from controlled clinical trials. For example, for an antiviral, this would include results from at least one well-designed, randomized, controlled clinical trial, and, in the case of laboratory studies, consistent evidence from comparative studies.

Category 2

Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from more than one centre), or from multiple time-series studies or dramatic results from uncontrolled experiments.

Category 3

Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Research Need

Area in which research is warranted.

Table 1: Cytomegalovirus diseases in the immunocompromised patient

Symptom	Neonate	SOT	HSCT	AIDS
Fever or hepatitis	+	++	+	+
Gastrointestinal symptoms		+	++	+
Retinitis	+	+	+	++
Pneumonitis		+	++	
Encephalopathy	++			+
Deafness	++			
Polyradiculopathy				+
Addisonian symptoms				+
Graft rejection		+		
Atherosclerosis		+		
Death	+		+	+

+ , prevalent; ++, very prevalent; SOT, solid organ transplant; HSCT, haematopoietic stem cell transplant; AIDS, acquired immunodeficiency syndrome.

Prophylactic versus Pre-emptive Approach to Preventing CMV Disease

The standard treatment for CMV disease is a 2–4 week course of IV ganciclovir. However, considering the morbid outcomes associated with CMV disease in the transplant patient, the preferred management strategy is to prevent disease from becoming established. There are two main strategies for prevention using anti-CMV drugs – prophylaxis and pre-emptive therapy. Both approaches have advantages and limitations, and controversy exists over which is the preferred method.^{11,12}

Antiviral prophylaxis involves the administration of anti-CMV compounds to all patients who are at risk of CMV disease (i.e. all patients except the D-/R- group). Currently, the anti-CMV compound is administered for 100 days after transplantation. This approach has significantly reduced the incidence and severity of CMV disease.⁴ Its advantages lie in its ease of administration (as it often utilizes orally administered compounds) and its ability to offer general protection against other herpesvirus infections and, as such, its association with a lower incidence of opportunistic superinfections.¹² However, the prolonged exposure to anti-CMV compounds (especially to compounds with suboptimal systemic levels) could theoretically result in the emergence of drug-resistant CMV.^{13,14}

In addition, antiviral prophylaxis could delay CMV-specific T-cell reconstitution and, thereby, increase the risk of late-onset CMV disease.¹⁵ Indeed, due to the widespread use of antiviral prophylaxis, the natural history of transplant-related CMV infection and disease has changed,^{4,16} with a subset of patients – mainly CMV-seronegative recipients of a seropositive solid allograft (so-called D+/R- SOT patients) and CMV-seropositive HSCT patients – developing late-onset CMV disease after the discontinuation of prophylaxis.^{16–19} This change in the epidemiology of transplant-related CMV raises the subject of whether the standard duration of antiviral prophylaxis should be reassessed in order to prevent late CMV disease. Lessons learned from studies with AIDS suggest that prolonged use of antiviral compounds may lead to drug resistance. Hence, prospective investigations into the optimal length of time for antiviral prophylaxis should include monitoring of drug resistance.^{20,21}

Pre-emptive therapy involves the administration of anti-CMV compounds (for varying periods of time)

before the onset of disease to patients with laboratory evidence of CMV infection. Theoretically, the reduced duration of exposure to antiviral compounds with a pre-emptive regime could decrease the likelihood of emergence of resistant CMV.^{11,14,17} However, to date, no studies have proven a decreased risk of antiviral resistance with pre-emptive therapy. In fact, a study by Limaye *et al.*²² found that the incidence of ganciclovir-resistant CMV infection was not significantly different between lung transplant patients who received prophylactic or pre-emptive (guided by pp65 antigen) ganciclovir therapy (three of 37 patients versus one of eight patients, respectively; $P=0.56$).²² Nonetheless, pre-emptive therapy – which is less likely to be associated with late-onset CMV disease – remains a preferred option for many clinicians. Its main drawback, at least for D+/R- patients, is the logistics of laboratory monitoring, which could lead to its failure to prevent early onset CMV disease.^{17,23}

Dynamics of CMV Infection: Implications for Treatment

DYNAMICS OF REPLICATION

Based on the time to appearance of cytopathic effects *in vitro*, CMV gained a reputation for being a slowly replicating virus. However, a study by Emery *et al.*²⁴ reversed this belief by demonstrating the replication of CMV as a dynamic process, with a viral doubling time of approximately one day *in vivo*. This study provided an important foundation of knowledge for studies on the importance of CMV load.

THE IMPORTANCE OF CMV LOAD

Viral load at the onset or peak of CMV reactivation correlates with the appearance of CMV disease in both HSCT and SOT patients.²⁵ A plot of probability of CMV disease against CMV load reveals a sigmoidal relationship between the two variables (Figure 1).²⁶ In the study by Cope *et al.*,²⁶ a marked increase in risk of disease was observed once the peak viral load in whole blood exceeded 5 log₁₀ genomes/ml. This represents a critical threshold where even relatively small increases in viral load correspond with rapid increases in the probability of disease – a phenomenon termed the ‘threshold concept of CMV disease’. Hence, one of the major goals of antiviral therapy is to reduce the direct effects of CMV by maintaining the viral load at a very low level or, if CMV has become established, to reduce the viral load as much as possible.

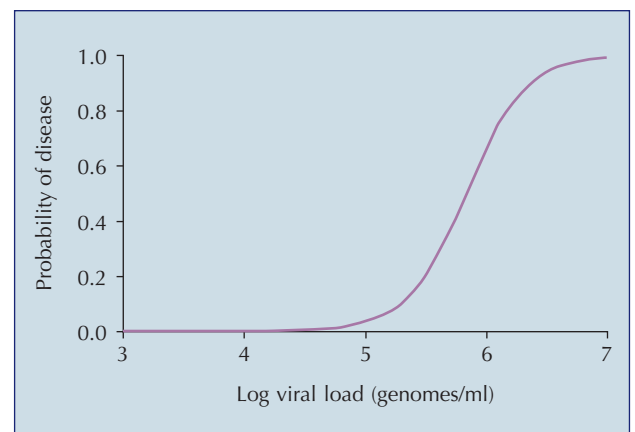


Figure 1: Sigmoidal relationship between probability of CMV disease and viral load.²⁶ Adapted with permission from Cope AV, Sabin C, Burroughs A *et al.* *Journal of Infectious Diseases* 1997;**176**:1484–1490. University of Chicago. © 1997 by the Infectious Diseases Society of America. All rights reserved.

The previous IHMF[®] management guidelines for CMV¹ supported the role of CMV load as a major risk factor for CMV disease.^{1,27} This was based on clinical studies that demonstrated initial and peak viral load and rate of change (i.e. rise) of viral load as early predictors of CMV disease or viraemia.^{1,25,28} Since then, a large body of data has been generated that further support the clinical value of CMV load, so as:

- To monitor response to antiviral therapy;
- To predict those who are likely to have recurrent disease;
- To optimize pre-emptive antiviral therapy.

MONITORING RESPONSE TO ANTI-CMV THERAPY

In studying CMV replication kinetics, both prior to and post-therapy in transplant patients, Mattes *et al.*²⁹ examined factors that may affect response to antiviral therapy (Table 2). It was found that the viral load at initiation of therapy, virus doubling time prior to therapy and the half-life of viral decline after initiation of treatment all affected treatment response (Table 3),²⁹ including the primary end-point of CMV PCR negativity at Day 14 of pre-emptive therapy (Table 2).

This study, which demonstrates that CMV load measurements are useful for monitoring response to antiviral therapy, complements the studies by Paya *et al.*²³ (Table 4) and Razonable *et al.*¹⁷ Together, these two studies indicate that patients with higher levels of CMV replication are less likely to respond to pre-emptive oral ganciclovir therapy. Considering that such viral persistence has the potential to give rise to CMV disease, these studies support the case for monitoring

Table 2: A comparison of ganciclovir with ganciclovir plus foscarnet (each at half dose) for pre-emptive therapy of cytomegalovirus infection in transplant recipients²⁹

Study details	Randomized, controlled		
Study population	48 CMV-seropositive renal, liver and HSC transplant patients		
Intervention	IV ganciclovir (5 mg/kg twice daily) versus half dose ganciclovir (5 mg/kg IV once daily)/half dose foscarnet (90 mg/kg IV once daily) combination		
Key results		Ganciclovir/ foscarnet, n=24	P value
	CMV PCR negative by Day 14	17 (71%)	0.12

CMV, cytomegalovirus; HSC, hematopoietic stem cell; IV, intravenous; PCR, polymerase chain reaction.

Table 3: Univariable risk factors for cytomegalovirus response to therapy²⁹

Risk factors	Odds ratio	Confidence interval (CI) 95% for odds ratio	P value
Initial viral load (per log ₁₀ higher)	2.39	1.05–5.44	0.038
Doubling time of viral load (per day increase)	2.95	1.28–6.82	0.01
Half-life of viral decline (per day increase)	3.01	1.45–6.25	0.003

Table 4: Pre-emptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients²³

Study details	Randomized, placebo-controlled			
Study population	69 liver transplant recipients with positive CMV PCR but no concomitant CMV disease or viraemia (by shell vial assay)			
Intervention	Oral ganciclovir (1 g three times daily) versus placebo for 8 weeks			
Key results		Ganciclovir (% n=35)	Placebo (% n=34)	P value
	CMV disease	0	12	0.022
CMV infection	3	21	0.003	

CMV, cytomegalovirus; PCR, polymerase chain reaction.

CMV load during antiviral treatment to help guide the intensity and duration of therapy.

IDENTIFYING PATIENTS AT RISK OF RECURRENT DISEASE

The clinical utility of viral load in identifying, at a very early stage, the patients who are at high risk of developing recurrent CMV disease after receiving standard therapy has also been demonstrated.

Humar *et al.*³⁰ obtained CMV load measurements at regular intervals from 52 SOT patients during IV ganciclovir therapy, including 12 (23%) with recurrent or relapsing CMV disease. The predictors of CMV disease relapse were time to viral clearance, which was longer among those who developed recurrent disease ($P=0.002$), and lack of viral clearance ($P<0.001$).

The study further demonstrated that CMV kinetics followed a logarithmic decay curve with a mean half-life of 8.8 days versus 3.17 days ($P=0.001$) among those who did and did not have recurrent disease, respectively. Therefore, using CMV load to assess initial response to therapy within the first few days of treatment has practical implications by allowing a clinician to identify, at an early stage, patients who will require more prolonged antiviral therapy.

The findings of this study³⁰ confirm the previous investigation by Sia *et al.*,³¹ wherein high CMV load at the onset of therapy, and persistently detectable CMV DNA at the end of therapy, were markers of CMV disease relapse.

OPTIMIZING PRE-EMPTIVE THERAPY

The aim of pre-emptive therapy is to identify patients with CMV infection as early as possible, in order to deploy therapy in a timely manner and so arrest viral replication and prevent the direct effects of CMV disease. CMV detection by molecular techniques, such as PCR, and non-molecular assays, such as antigenaemia, are acceptable methods of identifying patients with active CMV infection at an early stage (Figure 2).

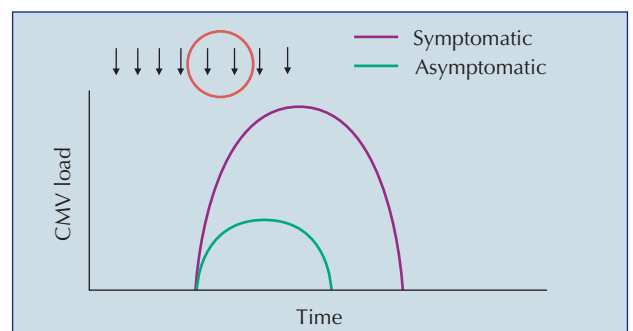


Figure 2: Effective pre-emptive monitoring of CMV.

It seems logical that a more frequent surveillance for CMV in blood samples from transplant patients will allow pre-emptive antiviral therapy to be initiated as early as possible. However, the optimal frequency of blood sampling for the different transplant populations remains to be determined. Currently, once-weekly blood sampling is often undertaken to determine the viral load when administering pre-emptive therapy. However, considering the very rapid replication dynamics of CMV, particularly in D+/R- patients, more frequent sampling may prove more effective. It has been proposed that twice-weekly sampling may be more appropriate in certain high-risk patient populations,^{17,23} and this warrants further research. It is clear, though, that whatever sampling frequency is deemed preferable, a rapid, sensitive detection system is essential (see next section).

Another remaining challenge pertaining to pre-emptive therapy is determining what CMV load is used as the cut-off point for initiating pre-emptive treatment. For the various CMV assays, there have been attempts at identifying the optimal cut-off value, but figures vary according to the patient group studied (e.g. related versus unrelated donors, type of transplant) and haematological procedures used (bone marrow versus peripheral blood stem cells). As such, no universal threshold exists to date and this remains a conundrum for those managing CMV infection and disease.

Advances in the Diagnosis of CMV Infection

METHODS CURRENTLY AVAILABLE FOR DIAGNOSING CMV INFECTION AND DISEASE

In the past, the standard methods for the diagnosis of CMV involved various culture techniques for CMV isolation, and antigenaemia assays which detect CMV pp65 antigen from peripheral blood leucocytes.³² However, as pre-emptive therapy has become a popular method of CMV disease prevention, a further challenge has arisen since the culture techniques do not fulfil the criteria of (and requirements for) guiding pre-emptive therapy^{1,33} as they:

- Lack sufficient sensitivity;
- Do not allow quantitation of viral load;
- Do not provide a high degree of reproducibility.

The antigenaemia assay is currently being used by many centres for the diagnosis of CMV infection and as a guiding tool for pre-emptive therapy. However, the lack of standardization and the subjective nature of its interpretation have limited its use.³²

The introduction of nucleic acid amplification-based methods for assessing CMV load provided a means of overcoming the limitations of non-molecular assays. A number of qualitative and quantitative methods are currently available, based on either PCR or nucleic acid sequence-based amplification (NASBA) technology.

Qualitative PCR assays are increasingly being replaced by quantitative assays,³⁴ which are used in the clinical setting to:

- Identify patients at risk of developing CMV disease;
- Provide rapid diagnosis of established CMV disease;
- Monitor response to antiviral therapy;
- Predict the risk of virological and clinical relapse;
- Serve as an early indicator of antiviral resistance.^{13,25,31,35-40}

The more widely used commercial assays include the COBAS AMPLICOR CMV Monitor³⁵ and the Murex Hybrid Capture Version 2.^{41,42} Numerous 'in-house' assays have also been designed using quantitative competitive and real time PCR technology (based on TaqMan®, LightCycler®, or similar platforms).^{32,43,44}

The development of PCR-based quantitative assays for CMV necessitates the standardization of these systems. Many of the commercially available tests vary with respect to the type of sample they utilize, the

number of DNA copies detected, amplification targets and calibration standards. Hence, there is a need for an international standard that is distributed by an independent quality control organization.

THE MOST APPROPRIATE BLOOD COMPARTMENT FOR DIAGNOSIS OF CMV DISEASE

Since the introduction of PCR for detecting CMV, debate has arisen as to which blood compartment is most suitable for CMV DNA detection. A prospective study by Razonable *et al.*⁴⁵ provided the first head-to-head comparison of four simultaneously obtained blood compartments – whole blood, plasma, peripheral blood leucocytes (PBL) and peripheral blood mononuclear cells (PBMC) – for the quantification of CMV DNA, using a standardized and automated quantitative assay, in 17 SOT and HSCT patients with 19 episodes of CMV disease and viraemia.

This study demonstrated that CMV DNA exists in high copy numbers in all four sample types tested, making them useful for prognostic purposes, for initiating pre-emptive therapy and for assessing response to therapy. However, whole blood was more sensitive for samples with low CMV DNA levels and it yielded CMV DNA levels 0.67 logs higher than with plasma ($P=0.0009$, Figure 3). This study, therefore, proposed that whole blood represents the optimal sample for CMV DNA quantification. The superiority of whole blood over plasma or other blood compartments was subsequently confirmed by other independent investigators.⁴⁶⁻⁴⁸

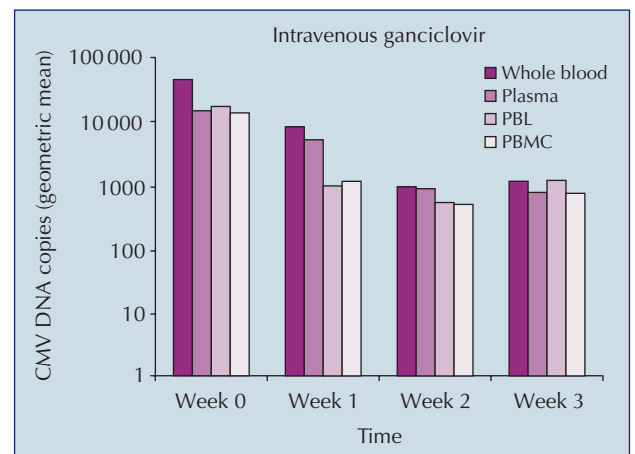


Figure 3: Weekly geometric mean CMV DNA copies per millilitre of whole blood and plasma and per 2×10^6 PBL and PBMC during 19 episodes of CMV disease and intravenous ganciclovir treatment.⁴⁵ CMV, cytomegalovirus; PBL, peripheral blood leucocytes; PBMC, peripheral blood mononuclear cells. Reproduced with permission from Transplantation 2002;73:968-973. © Lippincott Williams & Wilkins.

Prevention and Treatment of CMV Disease

Findings from a number of recent studies have prompted a revision of the recommendations for the prevention and management of CMV disease in SOT and HSCT patients.

NEWER FORMULATIONS OF ANTIVIRAL COMPOUNDS

New formulations of anti-CMV drugs have been developed that offer improved bioavailability and thus, a higher systemic concentration of active compound when compared to their predecessor oral compounds. Valaciclovir, the L-valyl ester prodrug of aciclovir, offers improved bioavailability of aciclovir over orally administered aciclovir.

Likewise, valganciclovir, the L-valyl ester prodrug of ganciclovir, greatly enhances the bioavailability of ganciclovir, resulting in serum ganciclovir concentrations that approach those achievable with IV doses of ganciclovir.⁴⁹ For this reason, many clinicians are opting to use valganciclovir, in preference to oral or IV ganciclovir, for anti-CMV prophylaxis. Hence, where these recommendations allude to the use of oral ganciclovir, clinicians may wish to use valganciclovir as the preferred formulation for anti-CMV prophylaxis.

TREATMENT OF ESTABLISHED CMV DISEASE
Intravenous ganciclovir remains the drug of choice for treating *established* CMV disease in SOT and HSCT patients.¹ In most cases, the duration of therapy is 2–4 weeks. However, viral load monitoring could determine the optimal duration of therapy.^{30,31,44}

The pharmacokinetic aspects of valganciclovir indicate that it may also be an alternative for the treatment of CMV disease.^{49–51} There has been extensive clinical experience of the use of valganciclovir in AIDS patients, where it was proven as effective as IV ganciclovir in treating newly diagnosed CMV retinitis.⁵² However, the clinical efficacy of valganciclovir for the treatment of established CMV disease in SOT and HSCT patients needs to be evaluated in a prospective, controlled, randomized clinical trial. Further research is also needed to assess whether adequate systemic levels of ganciclovir are achievable after valganciclovir administration in patients with poor gastrointestinal absorption, e.g. in patients with gastrointestinal graft-versus-host disease (GVHD). It is also important to define how valganciclovir doses can be modified to deliver appropriate control of CMV, especially in patients with renal dysfunction.

PREVENTION OF CMV IN SOT PATIENTS

Prophylactic therapy: The previous IHMF[®] management recommendations stated that ganciclovir is more effective than aciclovir in preventing CMV disease in liver and kidney transplant patients.¹ More recent studies, conducted by Rubin *et al.*⁵³ and Winston and Busuttill⁵⁴ provide further support for this recommendation.

Rubin *et al.*⁵³ compared the efficacy of oral ganciclovir versus low-dose aciclovir for the prevention of CMV disease in D+/R- SOT patients who had first

Table 5: Prevention of primary cytomegalovirus disease in organ transplant recipients with oral ganciclovir or oral aciclovir prophylaxis⁵³

Study details	Randomized, controlled, multicentre			
Study population	155 D+/R- kidney, heart and liver transplant patients			
Intervention	IV ganciclovir (5 mg/kg per day) for 5–10 days. Then, randomization to oral aciclovir (400 mg three times daily) or oral ganciclovir (1 g three times daily) for 12 weeks			
Key results		Oral ganciclovir, n=77	Oral aciclovir, n=78	P value
	CMV viraemia or disease by 6 months	25 (32%)	39 (50%)	<0.05
	Tissue invasive CMV disease	3/15 (20%)	10/21 (48%)	<0.05
	Time to CMV viraemia or disease (days)	291±13	212±17	<0.001
D+/R-, donor positive recipient negative; IV, intravenous; CMV, cytomegalovirus.				

received IV ganciclovir 5 mg/kg per day for 5–10 days (Table 5). This study found that oral ganciclovir was more effective than aciclovir at reducing the rate of CMV viraemia or disease at 6 months, including a significantly lower incidence of tissue-invasive CMV disease (Table 5).

The study by Winston and Busuttill⁵⁴ (Table 6) confirmed the superior efficacy of oral ganciclovir over oral aciclovir, in this case, in CMV-seropositive liver transplant patients. This study evaluated high-dose aciclovir (800 mg every 6 h) versus oral ganciclovir until Day 100, in patients who had first received IV ganciclovir 6 mg/kg per day from Day 1–14. A benefit was seen in the rate of CMV disease at 1 year with ganciclovir compared with oral aciclovir (Table 6).

Table 6: Oral ganciclovir versus oral aciclovir after induction with IV ganciclovir for long-term prophylaxis of cytomegalovirus (CMV) disease in CMV-seropositive liver transplant recipients⁵⁴

Study details	Randomized, controlled			
Study population	219 CMV-seropositive liver transplant patients			
Intervention	IV ganciclovir (6 mg/kg per day) Days 1–14. Then, randomization to oral aciclovir (800 mg every 6 h) or oral ganciclovir (1 g every 8 h) Days 15–100			
Key results		Oral ganciclovir, n=110	Oral aciclovir, n=109	P value
	CMV disease by 1 year	1 (0.9%)	8 (7.3%)	0.019
	Leucopaenia (<3 × 10 ⁹ /l)	38 (35%)	20 (18%)	0.009
IV, intravenous.				

Despite the benefits of oral ganciclovir seen in these trials, a considerable proportion of patients still develop CMV disease (32% in the study by Rubin *et al.*, Table 5),⁵³ suggesting that bioavailability of oral ganciclovir may not be clinically effective for many patients. While studies have suggested that IV ganciclovir may be more effective in this regard, recent data indicate that even IV ganciclovir does not completely prevent the occurrence of CMV disease upon the cessation of prophylaxis.^{55,56} A further study by Winston and Busuttill⁵⁵ compared the efficacy of prolonged IV ganciclovir and a strategy of sequential IV and oral ganciclovir in CMV D+/R- liver transplant patients (Table 7). There were no significant differences between the two regimens with regard to the rate of CMV disease by 1 year, nor the time to onset of CMV disease (Table 7).

Valganciclovir, which attains a serum ganciclovir level that is comparable to IV ganciclovir,⁴⁹ was recently compared with oral ganciclovir for CMV disease prevention in high-risk CMV D+/R- SOT patients. In a randomized, controlled, multicentre trial, Paya *et al.*⁵⁶ compared the safety and efficacy of valganciclovir (900 mg once daily) and oral ganciclovir (1 g three times daily) for the prevention of CMV disease in D+/R- kidney, heart, liver and pancreas transplant patients (Table 8). At 6 months after transplant, there was no significant difference between the incidence of CMV disease among patients administered valganciclovir and oral ganciclovir (12.1% versus 15.2%, respectively). By 12 months, the respective incidences were 17.2% and 18.4%. CMV viraemia during prophylaxis was significantly lower with valganciclovir (2.5% versus 10.4%; *P*=0.001) but this was comparable by 12 months. The time-to-onset of CMV disease and viraemia was

Table 7: Trial of sequential IV and oral ganciclovir versus prolonged IV ganciclovir for long-term prophylaxis of cytomegalovirus (CMV) disease in high-risk CMV-seronegative liver transplant recipients with CMV-seropositive donors⁵⁵

Study details	Randomized, controlled			
Study population	64 CMV D+/R- liver transplant patients			
Intervention	IV ganciclovir (6 mg/kg per day) Days 1–14. Then, randomization to oral ganciclovir (1 g every 8 h) or IV ganciclovir (6 mg/kg once daily Monday to Friday each week) Days 15–100			
Key results		Oral ganciclovir, n=32	IV ganciclovir, n=32	P value
	CMV disease by 1 year	3 (9.3%)	4 (12.5%)	NS
	Time to CMV disease	135 days	137 days	NR

IV, intravenous; D+/R-, donor positive recipient negative; NS, not significant; NR, not reported.

Table 8: Efficacy and safety of valganciclovir versus oral ganciclovir for prevention of cytomegalovirus disease in SOT recipients⁵⁶

Study details	Randomized, double-blind, double-dummy, multicentre, international			
Study population	364 D+/R- SOT (liver, kidney, heart, pancreas) patients			
Intervention	Valganciclovir (900 mg once daily) or oral ganciclovir (1000 mg three times daily) within 10 days (as soon as patient able to take oral medication) and up to Day 100 post-transplant			
Key results		Valganciclovir, n=239	Ganciclovir, n=125	
	CMV disease at 6 months* (%)	12.1	15.2	
	CMV disease at 12 months* (%)	17.2	18.4	
	CMV viraemia during prophylaxis [†] (%)	2.5	10.4	
	Median time to CMV viraemia	357 days	282 days	

*Incidence based on end-point committee defined CMV disease; [†]P=0.001; CMV, cytomegalovirus; SOT, solid organ transplant.

delayed with valganciclovir, and the rates of acute allograft rejection were generally lower with valganciclovir. Except for a higher incidence of neutropenia with valganciclovir (8.2% versus 3.2% for ganciclovir), the safety profile was similar for both drugs. Overall, the study showed that once-daily oral valganciclovir was as clinically effective and well tolerated as oral ganciclovir three times daily for preventing CMV disease in high-risk SOT patients.

Pre-emptive therapy: Since the previous IHMF[®] publication on this topic,¹ it has been demonstrated that oral ganciclovir is effective for the pre-emptive

treatment of asymptomatic CMV infection. A double-blind, randomized study by Paya *et al.*²³ (Table 4) demonstrated that, compared with placebo, pre-emptive therapy with oral ganciclovir (1 g three times daily) significantly reduced the incidence of CMV disease and viraemia in liver transplant patients who had CMV DNA detected by PCR. CMV infection and disease developed in 21% and 12% of placebo recipients, compared with 3% and 0%, respectively, among ganciclovir recipients. However, oral ganciclovir was unable to suppress high levels of viral replication¹⁷ and this may have implications for drug resistance and breakthrough CMV disease.

Subsequent to the last IHMF[®] published management recommendations on this topic, research has been undertaken to compare the efficacy and safety of IV ganciclovir and combination IV ganciclovir–foscarnet for the pre-emptive treatment of CMV infection. In a recent randomized trial conducted in a cohort of liver, heart and HSCT patients with asymptomatic CMV infection, Mattes *et al.*²⁹ (Table 2) observed that the combination of IV foscarnet and IV ganciclovir, each at half-doses, did not lead to a better control of viral replication when compared to full-dose IV ganciclovir. CMV PCR negativity within 14 days of pre-emptive therapy was observed in 17 of 24 patients (71%) receiving IV ganciclovir, compared with 12 of 24 patients (50%) receiving IV ganciclovir–foscarnet combination treatment. Moreover, there were significantly more patients in the IV ganciclovir–foscarnet combination treatment group who required the discontinuation of treatment or the reduction of drug dose as a result of toxicity (0 versus 29%; P=0.009). These *in vivo* data, therefore, do not support a synergistic interaction between ganciclovir and foscarnet.²⁹

PREVENTION OF CMV IN HSCT PATIENTS

Prophylactic therapy: As summarized in the previous IHMF[®] publication,¹ a number of clinical trials demonstrated the efficacy of prophylactic ganciclovir, administered up to Day 100 after transplant, in preventing CMV infection and disease in HSCT patients.^{57–59} However, such prophylactic therapy is associated with development of late-onset CMV disease and a significant risk of neutropenia. Hence, other antiviral compounds have been investigated for prophylactic use in HSCT patients. Aciclovir has a favourable safety profile compared with ganciclovir, but its clinical usefulness is limited by a low oral bioavailability. High-dose aciclovir was shown to reduce CMV infection and improve survival but it has no significant effect on the incidence of CMV disease.^{60,61}

Ljungman *et al.*⁶² conducted a head-to-head study of high-dose aciclovir and valaciclovir (which offers improved bioavailability of aciclovir) to investigate whether increased exposure to aciclovir could further suppress CMV replication and reduce the incidence of CMV disease. The patients received IV aciclovir (500 mg/m²) three times daily until Day 28 after transplant or after discharge and, thereafter, were randomized to receive oral valaciclovir (2 g) or high-dose oral aciclovir (800 mg) four times daily until Week 18 after transplant (Table 9). The study demonstrated that valaciclovir was significantly more effective than high-dose oral aciclovir in reducing the incidence of CMV infection. CMV infection or disease developed in 102 (28%) valaciclovir patients, compared with 143 (40%) aciclovir patients (P<0.0001). The incidence of CMV disease was low and did not differ significantly between the two treatments (5.5% and 3.5% in the valaciclovir and aciclovir arms, respectively). The safety profile was similar between valaciclovir and high-dose oral aciclovir, and survival did not differ significantly between the two treatments. This study, therefore, provides support for a new recommendation regarding the use of valaciclovir, in

Table 9: Randomized study of valaciclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants⁶²

Study details	Randomized, controlled, double-blind, multicentre, international			
Study population	748 CMV-seropositive (R+ or D+) recipients of allogeneic bone marrow-derived haematopoietic stem cells			
Intervention	IV aciclovir (500 mg/m ²) three times daily until Day 28 or after discharge. Then, randomization to oral valaciclovir (2 g) or aciclovir (800 mg) four times daily until Week 18			
Key results		Valaciclovir	Aciclovir	<i>P</i> value
	CMV infection/disease	102/366 (28%)	143/361 (40%)	<0.0001
	Survival	285/376 (76%)	278/372 (75%)	NS

CMV, cytomegalovirus; IV, intravenous; R+, recipient positive; D+, donor positive; NS, not significant.

preference to high-dose aciclovir, for antiviral prophylaxis in allogeneic HSCT patients.

Valaciclovir was also found to be comparable to IV ganciclovir as antiviral prophylaxis in HSCT patients. In a head-to-head trial conducted by Winston *et al.*⁶³ in patients who received an allogeneic bone marrow-derived HSCT, oral valaciclovir was compared with IV ganciclovir after patients had received initial prophylaxis with high-dose IV aciclovir prior to engraftment (Table 10). This study demonstrated that oral valaciclovir and IV ganciclovir had similar efficacies for the prevention of CMV disease and infection. CMV infection occurred in 12% of valaciclovir-treated patients and in 19% of IV ganciclovir-treated patients. CMV disease developed in two valaciclovir-treated patients and in one IV ganciclovir-treated patient. However, a significantly higher number of patients receiving valaciclovir prophylaxis were switched to other antiviral regimens, such as IV ganciclovir or foscarnet, because of possible or proven CMV infection and disease during the time of prophylaxis (12% for valaciclovir versus 5% for

Table 10: Randomized comparison of oral valaciclovir and intravenous ganciclovir for prevention of CMV disease after allogeneic bone marrow transplantation⁶³

Study details	Randomized, open-label, multicentre			
Study population	168 CMV-seropositive allogeneic bone marrow transplant patients			
Intervention	IV aciclovir (500 mg/m ² every 8 h) from Day 0 until engraftment. Then, randomization to oral valaciclovir (2 g four times daily) or IV ganciclovir (5 mg/kg every 12 h for 1 week, then 6 mg/kg once daily for 5 days per week) until Day 100			
Key results		Valaciclovir, <i>n</i> =83	Ganciclovir, <i>n</i> =85	<i>P</i> value
	CMV infection	10 (12%)	16 (19%)	NS
	CMV disease	2 (2.4%)	1 (1.2%)	NS

CMV, cytomegalovirus; IV, intravenous; NS, not significant.

ganciclovir, *P*=0.038). Hence, oral valaciclovir is an effective alternative to IV ganciclovir for prophylaxis of CMV disease after allogeneic HSCT, although it is associated with a higher likelihood of therapeutic interventions with other antiviral regimens.

Pre-emptive therapy: The previous IHMF[®] guidelines stated that pre-emptive therapy with IV ganciclovir was effective in reducing CMV disease and infection and, compared with prophylaxis, was less likely to be associated with neutropenia. Considering the neutropenia and leucopenia associated with ganciclovir use in HSCT patients,^{57,58,64,65} a number of studies have further looked at the potential of other antiviral drugs as alternative therapy in this group of patients.

Foscarnet appears to lack significant haematotoxicity.^{66–69} Reusser *et al.*⁶⁹ compared the efficacy of foscarnet and ganciclovir, initiated pre-emptively upon detection of CMV by antigenaemia assay or PCR in PBLs (Table 11). There were no significant differences between the two treatments with respect to the probabilities of patients remaining free of CMV disease or of death from any cause within 180 days of HSCT (Table 11). However, serum electrolyte abnormalities were significantly more common in the foscarnet group than the ganciclovir group; 22% versus 4% for hypocalcaemia (*P*<0.001), 18% versus 6% for hypomagnesaemia (*P*=0.006), 17% versus 6% for hypokalaemia (*P*=0.01) and 6% versus 0% for hypophosphataemia (*P*=0.01).

Table 11: Randomized multicentre trial of foscarnet versus ganciclovir for pre-emptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation⁶⁹

Study details	Prospective, randomized, open-label, multicentre			
Study population	213 allogeneic blood or marrow stem cell transplant patients			
Intervention	2 weeks with either IV foscarnet (60 mg/kg) or IV ganciclovir (5 mg/kg) administered every 12 h. If CMV infection remained detectable, patients received an additional 2 weeks of IV foscarnet (90 mg/kg) or ganciclovir (6 mg/kg) given once daily for 5 days per week			
Key results	End points	Foscarnet, <i>n</i> =110	Ganciclovir, <i>n</i> =103	<i>P</i> value
	Probability of event-free survival at Day 180	66%	73%	NS
	CMV disease at Day 180	5 (4.5%)	5 (4.8%)	NR
	Overall mortality	29 (26%)	23 (22%)	NR

CMV, cytomegalovirus; IV, intravenous; NS, not significant; NR, not reported.

At a reduced dose and when combined with half-dose IV ganciclovir, the use of foscarnet did not result in improved control of CMV infection, as compared with full-dose IV ganciclovir monotherapy, in SOT and HSCT patients.²⁹ Instead, combination therapy with half doses of IV ganciclovir and foscarnet was associated with higher incidence of drug toxicity, including renal dysfunction and electrolyte abnormalities.²⁹

Conclusions

The IHMF[®] management recommendations published here represent the culmination of a number of clinical

studies on CMV in transplant patients since the year 2000. Since that time, there have been considerable advances in our understanding of the diagnosis of CMV infection.

The availability of fully quantitative diagnostic methods has allowed us to monitor and quantify CMV more accurately, which has provided greater insights into CMV replication kinetics and disease pathogenesis. It has also allowed us to refine treatment algorithms for CMV, specifically in the context of pre-emptive therapeutic regimens, through the targeted use of antiviral compounds.

Clinical studies of antiviral therapies for the prevention of CMV infection and disease have been conducted, in both SOT and HSCT patients. Among these are studies with newer compounds, such as valganciclovir and valganciclovir, which offer improved bioavailability of the active antiviral component.

In SOT patients, prophylaxis with ganciclovir is more effective than aciclovir at preventing CMV disease. Valganciclovir provides a more convenient method of administering an effective prophylactic dose of ganciclovir to SOT patients, because the pill burden is lower (2 versus 12 each day for oral ganciclovir in a healthy adult) and does not require inconvenient infusion procedures.

In HSCT patients, prophylaxis with valganciclovir has

superior efficacy over oral aciclovir in reducing CMV infection and disease. Valaciclovir can be a useful alternative to IV ganciclovir as antiviral prophylaxis to reduce CMV infection and disease. Foscarnet is also an effective alternative to IV ganciclovir for the pre-emptive treatment of asymptomatic CMV infection.

The new antiviral drugs offer hope for further improving the management of CMV infection and disease, and research is needed to elucidate their use further. In particular, areas that need immediate investigation include the assessment of the clinical utility of valganciclovir for pre-emptive therapy in SOT and HSCT patients; as antiviral prophylaxis in HSCT and lung transplant patients; and as a treatment for established CMV disease.

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