REVIEW ARTICLE

Slaying the "Troll of Transplantation"—new frontiers in cytomegalovirus management. A report from the CMV International Symposium 2023

Camille N. Kotton[1] | Julian Torre-Cisneros[2,3] | Ibrahim Yakoub-Agha[4] |
The CMV International Symposium Faculty

[1]Transplant and Immunocompromised Host Infectious Diseases, Infectious Diseases Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[2]Maimónides Institute for Biomedical Research of Cordoba (IMIBIC)/Reina Sofía University Hospital/University of Cordoba (UCO), Cordoba, Spain

[3]CIBERINFEC, ISCIII - CIBER de Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain

[4]CHU de Lille, Univ Lille, Lille, France

Correspondence
Camille N. Kotton, Transplant and Immunocompromised Host Infectious Diseases, Infectious Diseases Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.
Email: ckotton@mgh.harvard.edu

Funding information
Biotest AG

Abstract

The 2023 International CMV Symposium took place in Barcelona in May 2023. During the 2-day meeting, delegates and faculty discussed the ongoing challenge of managing the risk of cytomegalovirus infection (the Troll of Transplantation) after solid organ or hematopoietic cell transplantation. Opportunities to improve outcomes of transplant recipients by applying advances in antiviral prophylaxis or pre-emptive therapy, immunotherapy, and monitoring of cell-mediated immunity to routine clinical practice were debated and relevant educational clinical cases presented. This review summarizes the presentations, cases, and discussions from the meeting and describes how further advances are needed before the Troll of Transplantation is slain.

KEYWORDS
cell-mediated immunity, CMV immunoglobulin, hematopoietic cell transplant, resistance, solid organ transplant, vaccines

1 | INTRODUCTION

The impact of the direct and indirect effects of cytomegalovirus (CMV) infection on posttransplant patients is well established, and over the past decade there has been a concerted effort to reduce the burden on patients by improving CMV prevention and treatment strategies. Despite significant advances, the risk of CMV infection remains a key concern in solid organ transplant (SOT) and allogeneic hematopoietic cell transplant (allo-HCT) settings.

During the 2023 International CMV symposium, Camille Kotton, Julian Torre-Cisneros, and Ibrahim Yakoub-Agha invited an international faculty to educate delegates on how to prevent CMV infection effectively and discuss how to improve treatment outcomes in transplant settings. Taking place in Barcelona during May 2023, the meeting provided an opportunity for delegates involved in CMV management to share insights and ideas both in person and virtually. Although improvements in CMV management were acknowledged, almost all delegates still saw CMV as a problem for their patients.

The first International CMV symposium took place in 2021 at a time when CMV management was still being conducted with SARS-CoV-2/COVID-19 restrictions in place. Paolo Grossi discussed the strain that COVID-19 put on delivery of CMV prophylaxis and treatment.[1] Physical distancing complicated prophylaxis, pre-emptive therapy, patient monitoring, and management of side effects. He explained that to address the challenges and simplify management, prophylaxis had been reserved for use in high-risk donor (D)+/recipient (R)- patients while pre-emptive therapy was more likely to be used in D+/R+ scenarios, although CMV DNA monitoring was challenging. Prophylaxis-related leukopenia, as well as delays in the laboratory test results used to inform pre-emptive therapy, were the main COVID-19-associated obstacles to CMV management experienced.[1] For those with previous CMV infection, developing severe COVID-19 came with a risk of reactivation as the corticosteroids required to manage SARS-CoV-2, as well as the need for mechanical ventilation and the high risk of bacterial coinfections, had the potential to trigger elevation of viral load.[2,3]

Since emerging from the pandemic, implementation of the advances in the prevention and treatment of CMV observed in the past decade has once again become a priority and this, as well as ongoing unmet needs (Table 1), will be discussed in this review.

2 | CMV PREVENTION: ANTIVIRAL STRATEGIES

2.1 | SOT setting

Mario Fernández-Ruiz described the burden of CMV in SOT. Poor outcomes are influenced by organ transplanted and serostatus of donors and recipients, with D+/R- associated with highest CMV disease risk.[4,5] Although pharmacological intervention reduces the incidence of CMV disease, patient outcomes are not always improved.[5] Ongoing risk has been attributed to indirect effects of the virus. Some indirect effects have the potential to affect all SOT recipients (e.g., bacterial and fungal infections or herpesvirus reactivation), while others are organ specific (e.g., chronic allograft nephropathy [kidney], cardiac allograft vasculopathy [CAV, heart], bronchiolitis obliterans [BOS, lung]).[6–8] Minimizing the indirect effects of CMV will have a substantial impact on outcomes in post-SOT recipients and should be considered when designing clinical trials to assess therapeutic options.

Choosing between universal prophylaxis and pre-emptive therapy (initiating antiviral therapy at the first signs of viral replication) is complicated by the fact that few randomized controlled trials (RCTs) have compared the two approaches. Both have benefits and weaknesses and identifying the most appropriate strategy at an individual level is key to improved outcomes. Emily Blumberg and Hannah Kaminski gave a brief overview of cases where the selection of strategy may not always be straightforward (Table 2).

2.1.1 | CMV prophylaxis in the SOT setting

Use of CMV prophylaxis to prevent CMV disease was first reported 25 years ago.[10–12] Evidence has since expanded, demonstrating how this approach prevents infection with other viruses, improves graft survival, prevents BOS—and other indirect effects—and improves survival rates.[4,13–17] Emily Blumberg explained that the established benefits of prophylaxis on direct and indirect effects of CMV are reflected in the guideline recommendations for use in SOT recipients and increased understanding regarding how to use prophylaxis.[18] Prophylaxis must be adapted to different circumstances, for example, an extended course of therapy should be considered in lung transplant recipients,[19] while management in patients with renal insufficiency can be complex.[18]

The key challenges when using prophylaxis are management of resistance due to prophylaxis choice or dosing, and treatment-emergent adverse events. Resistance risk varies depending on the serostatus of the donor and recipient and the type of organ transplanted. Overall risk of ganciclovir resistance in SOT recipients is 1.0%: 4.1% in D+/R- recipients, 11.9% in D+/R- lung transplant recipients, and 0.4% in D+/R- liver transplant recipients.[20] From an adverse event perspective, leukopenia is frequently experienced by patients receiving prophylaxis with ganciclovir or valganciclovir, with the incidence estimated at 30.5% in a recent meta-analysis.[21] Evidence supporting use of letermovir—which acts by inhibiting the viral terminase complex by encoding for pUL56—was limited in SOT at the time the most recent guidelines were published,[18] but data are now emerging supporting a potential role as prophylaxis in some SOT recipients. An RCT showed that letermovir was noninferior to valganciclovir for prophylaxis of CMV disease while significantly reducing leukopenia ($p < .001$).[22] Although encouraging, as letermovir has a low genetic barrier to resistance, its role in the SOT setting still needs to be established.[23–25]

Therefore, although universal CMV prophylaxis is standard of care in at-risk SOT, CMV disease remains the main challenge in organ recipients. Challenging cases of CMV prophylaxis in SOT recipients provided

TABLE 1 Unmet needs in cytomegalovirus management in posttransplant settings.

Burden	CMV remains a common problem posttransplant despite decades of treatment and diagnostic advances
Guidelines	Good guidelines are available but unable to personalize the best prophylactic and treatment course for individual patients
Antiviral management	Late CMV remains a major concern in high-risk patients at the end of prophylaxis
	Few RCTs have compared prophylaxis with pre-emptive therapy
	In allo-HCT, not all patients are eligible for standard CMV prophylaxis and appropriate management is still to be established in these patients
	Resistant/refractory CMV infection remains an issue for a small subset of patients
	Current prophylactic and therapeutic agents have issues of toxicity and cost, although letermovir as prophylaxis in kidney transplant recipients may be associated with less toxicity
Immune modulation	An "ideal" CMI assay is required before immune monitoring becomes part of routine clinical practice in all laboratories and a clinical tool for individualized decision making
	How to use CMVIG or CMV-specific T cells in clinical practice is still to be established
Vaccination	Lack of effective CMV vaccines remain a major deficit in the field

Abbreviations: allo-HCT, allogeneic hematopoietic cell transplant; CMI, cell-mediated immunity; CMV, cytomegalovirus; CMVIG, cytomegalovirus immunoglobulin; RCT, randomized controlled trials.

TABLE 2 The choice of prophylaxis or pre-emptive therapy is not always clear: patient cases.

Patient case	Induction	Immuno-suppressant regimen	Delegate preference for prophylaxis or pre-emptive therapy (% respondents)
54-year-old male with bilateral lung transplant for COPD (D+/R-)	ATG	Tacrolimus, MMF, prednisone	**Prophylaxis (88%)** A "typical" patient eligible for prophylaxis
41-year-old female with live donor kidney transplant for ESKD (D+/R+)	Basiliximab	Tacrolimus, sirolimus, prednisone	**Pre-emptive (65%)** Antiviral activity of mTOR inhibitors and a low-risk profile based on organ transplanted may justify pre-emptive therapy
58-year-old male, deceased kidney transplant for ESKD (D+/R+)	ATG	Tacrolimus, MMF, prednisone	**Prophylaxis (59%)** ATG induction depletes immune response so prophylaxis may be most appropriate
65-year-old male with heart transplant for ischaemic cardiomyopathy (D+/R+)	None	Tacrolimus, prednisone	**Pre-emptive (54%)** Marginal preference demonstrating choice is not always clear
24-year-old female with liver transplant due to autoimmune hepatitis (D+/R+)	None	Tacrolimus, prednisone	**Pre-emptive (86%)** A "typical" patient eligible for pre-emptive therapy
50-year-old male with liver transplant for end-stage liver disease (D+/R-)	None	Tacrolimus	**Prophylaxis (54%)** Reflects patients enrolled in pivotal pre-emptive study[9] but as high risk based on serostatus a more cautious approach may be adopted in clinical practice
68-year-old female with heart transplant for chemotherapy-induced cardiomyopathy (D-/R+)	Basiliximab	Tacrolimus, MMF, prednisone	**Pre-emptive (55%)** Choice may be less defined in D-/R+ patients

Note: For each case, delegates were given the choice of "prophylaxis," "pre-emptive therapy," or "not sure." The response selected by most delegates is shown in the table.

Abbreviations: ATG, antithymocyte globulin; COPD, chronic obstructive pulmonary disease; D, donor; ESKD, end-stage kidney disease; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; R, recipient.

by Osnat Shtraichman and Antoine Roux, and moderated by Marty Zamora, are summarized in Case Summaries 1 in the supplementary material.[26,27]

2.1.2 | Pre-emptive CMV therapy in the SOT setting

Hannah Kaminski explained that universal prophylaxis had been compared with pre-emptive therapy in four RCTs.[28–31] When included in a pooled meta-analysis, CMV infection was more likely to occur during pre-emptive therapy than during prophylaxis (40.4% vs. 24.7%), although CMV disease incidence was low and similar with both strategies (9.4% vs. 6.4%).[21] Included in this meta-analysis was an RCT comparing pre-emptive therapy with prophylaxis in D+/R- liver transplant recipients. The 12-month incidence of CMV disease was significantly lower with pre-emptive therapy than with prophylaxis ($p = .04$).[9] These results have been replicated in a real-world cohort,[32] which may explain why pre-emptive therapy is most likely to be used in D+/R- liver transplant recipients.

Immunosuppressive therapy (IST) is vital post SOT and response to pre-emptive antiviral therapies may vary depending on choice of IST.[33] A randomized, open-label study in seropositive kidney transplant recipients demonstrated greater benefit with pre-emptive therapy when ciclosporin-treated patients were receiving a mammalian target of rapamycin (mTOR) inhibitor, such as everolimus, rather than mycophenolic acid ($p < .0001$).[34] A clear lower rate of CMV infection has also been demonstrated in randomized trials of everolimus in heart transplant recipients.[35,36] mTOR inhibitors have anti-CMV properties, via direct inhibition of CMV replication in macrophages, indirect effects through improving cell-mediated immune response, and may decrease CMV infection and disease in seropositive recipients.[18,34,37] The kidney transplant study also demonstrated that everolimus, with pre-emptive therapy, reduced the need for ganciclovir or valganciclovir treatment for CMV DNAaemia ($p = .0007$).[34]

2.2 | Allo-HCT setting

David Beauvais highlighted the importance of understanding the risks for CMV infection in the allo-HCT setting. The major risk factor for CMV infection post HCT is serostatus, with the risk being highest in R+ individuals.[38] Other risk factors include negative serostatus of the donor, human leukocyte antigen (HLA) mismatch, intensity of conditioning regimen (e.g., myeloablative), and whether the recipient develops graft-versus-host disease (GvHD).[39] A score based on six weighted factors—donor serostatus, donor type (identical sibling or unrelated), conditioning regimen (reduced intensity or myeloablative), use of total body irradiation, use of antithymocyte globulin (ATG), and use of mycophenolate mofetil (MMF)—identified four risk groups (low, intermediate-low, intermediate-high, high) each with a distinct risk of CMV infection which can be used to guide management.[40]

Letermovir is approved as universal prophylaxis for CMV-positive allo-HCT recipients up to day 100 posttransplant based on the findings of a phase 3 study.[41,42] However, not all patients are eligible for letermovir.

2.2.1 | Patients eligible for letermovir

In the pivotal letermovir trial, a significant reduction in CMV infection incidence compared with placebo was described ($p < .001$), and this result has since been confirmed in real-world settings.[42,43] However, despite being approved as universal prophylaxis, not all patients obtain the same level of benefit. David Beauvais described how the previous risk score had been used to identify low- or high-risk patients and investigate the efficacy of letermovir in a risk-adapted strategy.[44] Limited use of letermovir in patients at low risk was shown not to impair clinical outcomes, thus reducing potential overtreatment, while the benefits of letermovir were demonstrated in patients at high risk. One of the challenges experienced by clinicians using letermovir is the development of transient increases in CMV DNA known as "blips," the clinical relevance of which is not always clear. Additional diagnostic methods (e.g., virus isolation and degradation of free-floating viral DNA) should be used to dissect between noninfectious and infectious CMV DNAaemia under letermovir.[45] In the risk-score analysis, pre-emptive therapy in individuals with CMV DNA $\geq 3.5 \log_{10}$ IU/mL distinguished between transient blips and clinically relevant infection.[44]

Letermovir is approved for use in patients up to day 100 post HCT, and there have been reports of late infection once treatment is discontinued, which are attributed to the delay in T-cell reconstitution during antiviral therapy.[44,46,47] Late infection occurred mainly in patients receiving corticosteroids after week 14 post HCT or in those with early CMV infection (before week 14).[44] An extended course of letermovir could be appropriate in this group of patients.

2.2.2 | Patients ineligible for letermovir

Letermovir is standard prophylaxis after allo-HCT,[41] but some patients are ineligible. The options open to them were described by Guido Kobbe. Ineligible patients include those with mismatched serology (R- and D+); patients with either severe liver dysfunction or moderate hepatic impairment combined with moderate or severe kidney dysfunction; patients intolerant to letermovir; and patients receiving drugs likely to result in severe interactions (including cytochrome P450 3A substrates or organic anion transporter polypeptide 1B/3 inductors or inhibitors).[41] As letermovir is not approved for secondary prophylaxis, or for use beyond 100 days post HCT, a substantial number of initially letermovir-eligible patients may also require alternative management strategies.

Pre-emptive antiviral therapy may be useful in ineligible patients, as an early RCT demonstrated that event-free survival was similar with foscarnet and ganciclovir.[48] However, foscarnet was associated with kidney failure and electrolyte disturbances, while hemotoxicity was reported with ganciclovir. Subsequent studies have shown an improved pharmacokinetic profile with oral ganciclovir compared with the

intravenous option.[49] Guido Kobbe concluded that pre-emptive therapy alone may not be sufficient and suggested that combination antiviral and immunomodulatory therapy may be suitable for R- patients.

3 | CMV PREVENTION: IMMUNOLOGICAL STRATEGIES

3.1 | The role of the immune system in CMV management

The immune response to CMV infection involves the innate and adaptive immune systems. Primary infection of CMV activates the innate immune system, resulting in release of inflammatory cytokines from monocytes, macrophages, and dendritic cells.[50] CMV-specific cluster of differentiation (CD) 8+ T cells appear after the peak of CMV replication and synthesize interferon gamma (IFNγ) as well as other T-helper 1-type cytokines. CMV-specific T cells account for 10% of peripheral T cells in healthy subjects and up to 40% in the elderly.[51] CD8+ T cells react against many structural viral proteins including those that are immunodominant such as the viral immediate-early (IE) 1 protein (encoded by UL123), IE2 protein (encoded by UL122), and pp65 (encoded by UL83).[51] As developing high frequencies of CD8+ T cells against some of these proteins may provide protection from CMV disease, the antigens are utilized in cell-mediated immunity (CMI) assays discussed in Section 3.2.

María E. Martínez-Muñoz explained that T-cell responses are often impaired in allo-HCT recipients and that a lack of CMV-specific cytotoxic T cells (CTLs) has been shown to correlate with risk of reactivation, CMV disease, and mortality.[52,53] The impaired response is associated with the lymphodepleting effect of conditioning regimens, graft manipulation (T-cell depletion), and the use of IST to avoid graft failure and GvHD.[50] After allo-HCT, early T-cell reconstitution occurs via peripheral expansion of mature naïve and memory T cells that are transferred in the graft, but these have a limited T-cell receptor repertoire.

3.2 | Role of CMI in management of CMV

CMI can be used to guide clinical decision making in the posttransplant setting. Although an inverse relationship between CMV-specific CMI and CMV clearance has been observed in SOT,[54] the wide range of specific CMV T-cell frequencies (e.g., detection of IE1 and pp65)[55] between patients and varying antigen kinetics means that the results are not easy to interpret. As immune response may also differ between SOT and allo-HCT settings, adoption of CMI may vary between patients and transplant settings.

Absolute lymphocyte count has historically been used to measure the immune response in posttransplant recipients, and this remains the most accessible way of assessing immune status.[56] However, several CMI assays based on measurement of IFNγ or other cytokines in response to stimulation can provide information about the specific response to CMV. IE1 and pp65 are the antigens most frequently used to stimulate the immune response in CMV-specific assays.[55] High levels of CMI indicates adequate T-cell immunity while patients with low CMI are at risk of CMV infection.

Roy Chemaly reviewed the commercially available research tools.[57] A commercially available enzyme-linked immunosorbent assay (ELISA; QuantiFERON-CMV; Qiagen Inc.) detects release of IFNγ in whole blood following stimulation by CMV peptides. The ELISpot assay, a highly sensitive immunoassay, measures the frequency of CD4+ and CD8+ T cells producing IFNγ in response to CMV-specific peptides or whole proteins. Although more robust than ELISA, a specific reader is required, and commercial assays (T.Spot.CMV, Oxford Diagnostics; T-Track, Lophius Bioscience/Mikrogen GmBH) are not universally available. Flow cytometry can also be used to run a CMV T-cell immunity panel and obtain responses by intracellular cytokine staining. The advantage of this assay is that it can be expanded to include a range of cytokines and cell surface molecules to provide quantitative and qualitative measurements of CMV-specific T cells as well as distinguishing between CD4+ and CD8+ response. In major histocompatibility (MHC)-multimer-based assays, peptide-specific T cells are stained using peptide-conjugated MHC class 1 tetramers or pentamers to determine CD8+ T-cell responses.[57] These strategies may also allow comparative analysis of lymphocytes restricted by shared, donor- and host-specific HLA to track thymic-independent CMV-specific reconstitution.[58] However, this method requires knowledge of HLA type and, like intracellular staining, needs fluorescence-activated cell sorting facilities.

The goal of CMI assays is to personalize the management of CMV to avoid excess treatment and toxicity. Therefore, an ideal assay needs a positive cut-off applicable for most patients and should be able to be performed in any laboratory. Currently the tests can be expensive, and costs incurred need to be balanced against the savings associated with less viral-load testing and reduced use of antiviral prophylaxis. These ongoing challenges contribute to low uptake reported in a survey across 152 European Society of Blood and Marrow Transplantation centres where only 11% of centres were using CMI within clinical or experimental practice (24% ELISA, 88% ELISPOT, 41% flow cytometry) in September 2021.[56]

3.2.1 | CMI in SOT recipients

For CMI to be adopted as routine clinical practice, the prediction capability needs to be established and appropriate thresholds identified. Oriol Bestard explained that in SOT recipients, CMI has been useful in differentiating CMV risk in R+ transplant patients,[59,60] although in R- individuals, where a positive CMI does not mean that CMV will not develop, use is less established. T.Spot.CMV (IE1 and pp65) identified R+ individuals at high risk of developing CMV infection and monitoring at posttransplant day 15 further defined risk of CMV infection.[60] Protection was largely due to immune activity against IE1 although use of T-cell depletion or induction therapy reduced the level of protection. This approach seems promising; however, a fixed threshold that clearly distinguishes between low- and high-risk patients has not

been identified and many patients fall into an intermediate "gray" zone.[61,62] Oriol Bestard described ongoing work where IE1 and pp65 responses are used to produce a continuum of risk that clearly identifies those at low and high risk to allow appropriate management. For patients in the intermediate zone, the approach identified a subgroup who develop CMV disease despite favorable CMI. The strategy has been applied to previous cohorts of patients participating in different studies (e.g., PROTECT[63] and RESPECT[60]) as well as in new patient cohorts, and results are anticipated shortly. Oriol Bestard concluded that CMI for CMV immune-risk stratification opens a door for personalized medicine in the field of SOT (Figure 1).

3.2.2 | CMI in allo-HCT recipients

The REACT study showed that CMI could have a role in the allo-HCT setting.[64] ELISPOT was used to identify HCT recipients at risk of clinically significant CMV infection using thresholds based on the number of "spots" to IE1 and pp65 stimulation. CMI was a significant and independent predictor of clinically significant CMV infection. A patient's CMV-CMI at a specific timepoint could be used to tailor both the duration and intensity of CMV monitoring and the duration of antiviral therapy or prophylaxis. Multivariate analysis identified sex, race, and use of ATG or corticosteroids as additional risk factors for clinically significant infection. Analysis of the REACT dataset is ongoing to determine whether change in response to the IE1 and pp65 antigens, rather than absolute count, could be a useful predictor of infection.

As letermovir delays the immune response, T-cell responses are higher with pre-emptive therapy than with prophylaxis.[9,47] It may be that the advance in CMV prophylaxis has limited the applicability of one of the other key advances—using CMI to guide treatment. Roy Chemaly highlighted that there was still a need to understand more about the immune response given that not all patients respond to letermovir[42] and suggested that CMI could provide valuable clinical insights.

Another focus of CMI research is whether CMI can predict outcomes in low-level CMV reactivation. A small study demonstrated that recipients with a low CMI were 8.3 times more likely to experience CMV progression than those with a high CMI ($p < .0001$).[65] In this study, corticosteroid use was also a predictor of progression ($p < .002$).

Raffaella Greco contributed to the discussion on use of CMI in the allo-HCT in her clinical case (Case Summaries 2 in the supplementary material) in a session moderated by Martina Sester and Michele Malagola.[58,66,67] She concluded that CMI may help to improve risk stratification of patients, although there is still a need to establish which assay should be used and when.

3.3 | Immune system modulation in CMV management

3.3.1 | CMV-specific CTLs

María E. Martínez-Muñoz explained how adopting transfer of CTLs after allo-HCT has the potential to induce rapid reconstitution of T-cell-mediated immunity against CMV, an approach that is included in guidelines for allo-HCT and SOT patients with recurrent or resistant CMV.[18,68]

Most CTL manufacturing methods rely on ex vivo stimulation, activation, and expansion of antigen-specific T cells. Early data demonstrated that viral immunity can be restored in immunodeficient allo-HCT recipients with CTLs and that the approach has a favorable safety profile with limited incidence of GvHD.[69,70] These data were encouraging, but generating the CTLs took between 8–12 weeks and therefore had limited applicability in clinical practice. Since then, advances in the manufacturing process, the use of third-party donors with limited incidence of GvHD and the generation of virus-specific T-cell banks with "off-the-shelf" products have made this therapeutic option more attractive. It has been shown that a small number of carefully selected third-party donors, selected according to the expression of high frequency HLA antigens in a given population, provide CTLs to form a source bank with broad patient coverage, reducing the risk of rejection or GvHD. A bank of 17 CMV-specific CTLs selected for expression of six core HLA antigens, provided treatment for 28 allo-HCT recipients with refractory infection, resulting in a complete response rate of 79% at 1 year, with only five patients requiring antiviral therapy. The safety profile was good, with only two patients developing GvHD despite a median HLA match between CTLs and the recipient of two out of six antigens.[71,72] Similarly, a bank of eight CMV-positive third-party donors provided a CTL product that was HLA matched for at least two antigens covering almost 97% of the local US patient population. Ten allo-HCT recipients infused for persistent/refractory CMV infections or disease achieved some degree of response with 70% having a complete response.[73]

María E. Martínez-Muñoz explained that there is less experience in the SOT setting, and, in general, results have been less convincing. She suggested that this might be because there is a more qualitative than quantitative immune dysfunction in SOT compared with allo-HCT due to a protracted (less lymphodepleting) immunosuppressive therapy and there is also a concern about the risk of graft rejection or low persistence of allogeneic CTLs.

Classification of CTLs as Advanced Therapy Medicinal Products has cost and logistical implications and has prevented the development of individualized therapy in CMV. However, the creation of CTL banks and particularly the generation of "multi-specific" CTLs might enable a widespread use of this type of therapy in the future.

3.3.2 | Cytomegalovirus immunoglobin

Andreas Zuckermann described how cytomegalovirus immunoglobin (CMVIG) has an increasing role in the management of CMV. CMVIGs were first developed in the 1970s with the first evidence of significantly decreased virologically confirmed CMV syndrome published in 1987.[74] To obtain CMVIG, plasma is collected from donors with high anti-CMV IgG; the commercial CMVIGs currently available have enhanced immunomodulatory properties and exert greater inhibitory activity on allogeneic T-cell proliferation and cytokine production than the CMVIGs initially developed.[75]

(A)

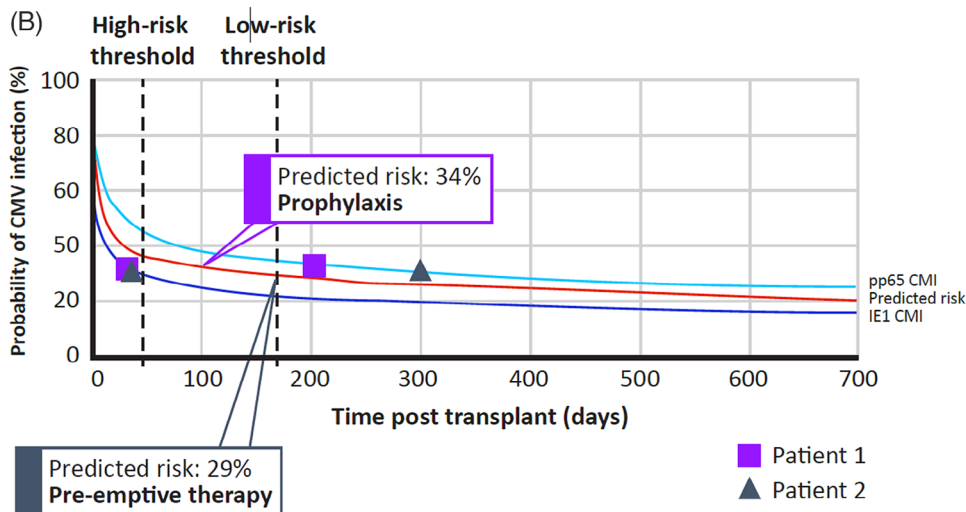| IE-1 risk zone	pp65 risk zone	Predicted overall risk	Risk category	Strategy
Low	Low	3.5%	Low risk	No preventative strategy
Intermediate	Low	18% (between thresholds)	Low risk	Pre-emptive PCR
High	Low	29% (close to low threshold)	Intermediate risk	Pre-emptive PCR
High	Low	34% (close to low threshold)	Intermediate risk	Prophylaxis
High	High	75%	High risk	Prophylaxis

FIGURE 1   (A) Individuals can have IE1 and pp65 responses that fall into different risk categories. Using both results can generate a continuum of risk that can guide appropriate management (example risks shown). (B) Two patients in the intermediate risk category where different management strategies would be appropriate based on calculation of risk from IE1 and pp65 responses and proximity to risk thresholds. Concept described by Oriol Bestard (unpublished). CMI, cell-mediated immunity; CMV, cytomegalovirus; IE-1, intermediate-early 1; PCR, polymerase chain reaction.

CMVIG has now been studied in different SOT settings and has been shown to prevent CMV disease. In an early meta-analysis, the benefit of prophylactic CMVIG was demonstrated on survival, CMV-associated death as well as infection and disease; however, in a later meta-analysis although a small benefit was observed in CMV infection it was smaller than seen previously.[76–78] Andreas Zuckermann speculated that this was due to wider routine use of prophylaxis. In addition, he pointed out that CMVIG may also contribute to a reduction in the risk of posttransplant lymphoproliferative disease.[79,80]

Focusing on his specialty of heart transplantation, Andreas Zuckermann described how the benefits of CMVIG had been shown even in aggressively immunosuppressed recipients.[81] However, as D+/R- patients were still at risk of CMV infection and disease, CMVIG alone may not be an appropriate prevention strategy. This observation opened up the option of combination therapy with antiviral prophylaxis and CMVIG and a subsequent study demonstrated than CMVIG combined with ganciclovir was able to abolish CMV-related death and prevent CMV disease in high-risk heart transplant recipients.[82]

High rates of response have also been reported in heart or lung transplant or allo-HCT recipients (66%–78%).[83–85] However, given the complexity of care in these patients it is not possible to attribute all the benefit to use of CMVIG. Patient cases where CMVIG was used in allo-HCT recipients were provided by Michele Malagola and Lana Desnica and describe how CMVIG was only part of the management regimen used to control CMV and GvHD in sessions moderated by Ibrahim Yakoub Agha, Martina Sester, and Michele Malagola (Case Summaries 3 in the supplementary material).

Current SOT guidelines, as well as the newly updated International Society for Heart and Lung Transplant guidelines, explain that CMVIG is used by some experts in D+/R- heart and/or lung transplant recipients although a specific recommendation is not provided.[18,86] Andreas Zuckermann concluded that more needs to be learned about how to use CMVIG in SOT and allo-HCT recipients and a multicenter, prospective, noninterventional study in Europe currently in progress will help to elucidate how CMVIG is being used in the real world.

4 | MANAGEMENT OF REFRACTORY OR RESISTANT CMV

Patients with refractory or resistant CMV have higher rates of hospitalization, graft loss, and mortality than patients who respond to initial treatment without developing resistance.[20,87] Nassim Kamar explained that refractory CMV is CMV viremia that increases after at least 2 weeks of appropriately dosed antiviral therapy while patients with persistent detectable viral load after at least 2 weeks of therapy have probable refractory CMV infection.[88] For resistant CMV to be confirmed, a viral genetic alteration should be evident to explain the decreased susceptibility to antiviral medication. The most frequently reported mutations relate to amino acid substitutions in UL97 (ganciclovir, valganciclovir, maribavir) and in UL54 (ganciclovir, valganciclovir, cidofovir, foscarnet, cidofovir, brincidofovir).

Recurrent CMV disease has been reported in 19%–30% of SOT recipients,[89,90] with serostatus and type of organ transplanted influencing risk of recurrent infection with highest rates seen in D+/R- scenarios and in lung transplant recipients.[89]

Resistance to antiviral therapy used for CMV is infrequent with rates being generally below 5%.[91,92] In a recent European Society for Organ Transplantation (ESOT) survey, 80% of centres reported that fewer than 1% of patients develop resistance;[93] however, despite these low levels, given the poor outcomes associated with resistance, it is important to identify those at highest risk. Resistance can occur in both SOT and allo-HCT recipients with risk factors varying between the two settings.[88] However, prolonged antiviral drug exposure and inadequate antiviral therapy dosing/delivery are common to both. In SOT, D+/R- and lung transplant recipients are most likely to develop resistance, while in allo-HCT recipients, risk is highest in D-/R+ recipients and where haploidentical, allogeneic, or cord-blood HCT is used.[18,88]

In SOT recipients, the ESOT survey identified that high-dose intravenous ganciclovir was most likely to be used to treat resistant CMV with foscarnet, cidofovir, and CMVIG (in combination with antiviral agents) also being used in substantial proportions of patients.[93] Benefit has been shown, but the risk of relapse and/or side effects (neutropenia for ganciclovir; renal impairment for foscarnet and lack of efficacy for cidofovir) means that treatment for these at-risk patients remains an unmet need.[87,88,93,94]

The new antiviral agent, maribavir, acts by inhibiting the UL97 protein kinase and has provided an alternative treatment option for patients with refractory or resistant CMV.[95] CMV viral clearance has been achieved within 6 weeks in both SOT and allo-HCT recipients[96] and significantly more patients achieved clearance with maribavir than standard of care.[97,98] The benefits of maribavir have been demonstrated irrespective of transplanted organ and whether the patient had refractory or resistant CMV.[98]

Although maribavir has provided a valuable treatment option for previously difficult to manage patients, unmet needs remain, not least in the centres where the agent is not available. Where maribavir can be used, response rates are approximately 56% at week 8, but by week 16 this has reduced to 19% so a substantial proportion of patients will require additional therapy.[98] Treatment-emergent UL97 substitutions have also been observed showing that there is a risk of resistance with maribavir and adverse events, especially dysgeusia that affected 37% of patients in the phase 3 trial.[95,98]

Nassim Kamar concluded that the best treatment option is still to be established for these complex patients. Patient cases demonstrating the challenge of managing CMV in patients with refractory and resistant CMV were provided by Nikolaus Kneidinger, Karthik Santhanakrishnan, and Sophie Alain and moderated by Martina Sester, Michele Malagola, Udo Boeken, and Reem Almaghrabi (Case Summaries 4 in the supplementary material).[99]

5 | THE FUTURE OF CMV MANAGEMENT

The outcomes for patients at risk of CMV post transplant have improved in recent years, but CMV remains the most common complication affecting patient survival after transplantation. To address the negative impact of CMV on transplant recipients, Ligia Pierrotti explained that current research is focused on identifying new antiviral therapies with improved adverse event and resistance profiles as well as developing anti-CMV vaccines.

5.1 | Novel antiviral agents

The first antiviral agent, ganciclovir, which acts on the CMV DNA polymerase, was approved in 1989. This enzyme within the replication cycle was the target of all approved antivirals until letermovir (terminase inhibitor) and maribavir (protein kinase inhibitor) were approved.[100,101] The CMV replication cycle provides many other potential therapeutic targets for intervention, including those that influence viral entry, genome replication, gene expression, or virion assembly and egress[100]; however, few have been evaluated in humans, with animal studies being frequently aborted due to safety concerns.

Ligia Pierrotti explained that currently only two novel antivirals were of interest, brincidofovir, and filociclovir.

Brincidofovir, a lipid conjugate of cidofovir and 3-hexadecyloxy-1-propanol, has improved intracellular active drug delivery and in vitro antiviral potency versus cidofovir.[102] Although CMV-related events were reduced with brincidofovir compared with placebo in a Phase 2 trial,[103] the phase 3 study failed to show a benefit primarily because of severe gastrointestinal toxicity and a high incidence of GvHD.[104] Filociclovir, a second-generation methylenecyclopropane nucleoside analogue, has favorable bioavailability and is up to 10 times more effective than ganciclovir at controlling viral replication.[105] The resistance profile of filociclovir is distinct to that of ganciclovir and maribavir, although some cross resistance has been demonstrated to ganciclovir and foscarnet.[106] As activity was retained against a panel of ganciclovir-resistant human CMV isolates, filociclovir may be a useful alternative therapy for patients with resistant CMV.

Several compounds well characterized in preclinical or clinical studies of other diseases have been investigated in the CMV setting. Ligia Pierrotti concentrated on the antimalarial artemisinin compounds and metformin which targets host electron transport chains. Artesunate has similar efficacy to ganciclovir and may have a synergistic effect when used in combination with other antiviral agents.[107,108] In a retrospective, single-center study in allo-HCT recipients, artesunate effectively controlled CMV replication in 74% of patients, with CMV being cleared in 19% of episodes. Treatment was tolerated by 22 patients; however, three developed hemolysis requiring artesunate to be stopped.[109] Metformin targets host cell mitochondrial metabolism and although most drugs targeting the mitochondria are too toxic for therapeutic use, the safety profile of metformin has been established previously in patients with type 2 diabetes mellitus. In the CMV setting, metformin has been shown to reduce CMV titre.[110]

5.2 | Vaccination

Despite 50 years of research, Ligia Pierrotti described how there was still no commercially available vaccine for CMV, and she suggested that inducing immunity in immunosuppressed individuals will be an ongoing challenge. Due to multiple CMV immune-evasion strategies, CMV can remain latent in myeloid cells for a lifetime, and vaccine candidates will need to provide protection exceeding that of natural infection by enhancing both humoral and cellular immune response in order to be effective.[111] Currently there is a critical lack of knowledge about the correlates of protective immunity in different clinical settings and how to evaluate efficacy in clinical trials.[112]

Eight vaccine candidates being tested in clinical trials were described by Ligia Pierrotti, with the majority being in early phases of development. Safety and immunogenicity have been demonstrated with several candidates, but prevention of infection has been infrequently reported. ASP0113, a DNA-based vaccine containing two plasmids encoding human CMV glycoprotein B (gB) and pp65, has been studied in a Phase 3 trial; however, as neither overall mortality rates nor CMV disease were reduced 1-year post transplant, and a potent immune response was not elicited, development was not continued.[113] Of the candidates still in development, subunit vaccines have shown promise with prevention of primary infection demonstrated in 50% and 43% of postpartum women and adolescent females, respectively, using a gB vaccine.[114,115] In the transplant setting, gB antibody titres increased, and the duration of viremia and the number of days of prophylaxis required were both significantly reduced compared with unvaccinated recipients.[116] Although this vaccine is no longer in development, a trial investigating a newer subunit vaccine combining gB and pentamer antigens is currently recruiting (NCT05089630).[117,118] In allo-HCT recipients, intramuscular injections of a pox virus vectored vaccine, Triplex, reduced risk of serious adverse events or grade ≥3 adverse events during the first 100 days post-allo-HCT by 54% and vaccinated individuals had fewer CMV reactivations.[119] High levels of CMV-specific T cells were demonstrated and the adverse event profile was similar to placebo. A chimeric peptidic vaccine, CMVPepVax, demonstrated higher rates of relapse-free survival and significantly less CMV reactivation compared with an observation group in a phase 1 trial of allo-HCT recipients.[120] It is currently being studied in a phase 2 study (NCT02396134).[121] A peptide vaccine, CMVPepVac, is also promising as an immune response was elicited in 50% of patients and no responder experienced reactivation in the 18 months post renal transplant,[122] but further studies in larger cohorts are required. Ligia Pierrotti described how live-attenuated, RNA-based and virus-like particle vaccine platforms are still in the early stages of development.

Vaccines could play an important part in future management of CMV by supporting early interruption of antiviral therapy and thus minimizing the risk of toxicity and resistance. Identifying novel candidates as well as continuing to study the benefits of currently available vaccines should be a priority. Once licensed, specific recommendations on how to use vaccines in donors and recipients will be required.

6 | HAS THE TROLL BEEN SLAIN?

The concept of the "Troll of Transplantation" was first introduced by Henry H. Balfour in 1979,[123] and progress has been in managing the troll that is CMV post transplant. However, further improvements are still required in order to slay the troll. In his keynote lecture, Luciano Potena's take-home message was that the tools are now available to develop a personalized approach to management of transplant recipients.

The potential role for CMI had been discussed during the symposium, but based on the data presented it is clear that more information is required before CMI becomes a routine way to predict outcomes and guide decision making. Once CMI is established it may become a reliable way of identifying high-risk patients and linking them to appropriate therapy and a consistent method of identifying low-risk patients to minimize over-medication.

Antiviral therapy remains limited by the risk of adverse events and potential risk of resistance with prolonged prophylaxis potentially resulting in late-onset viremia and graft loss.[18,68] However, increased knowledge about the influence of different induction and IST regimens

on CMV-related outcomes is helping to ensure that patients receive an optimized post-transplant management regimen. The future management of CMV may rely increasingly on prolonged prophylaxis or immunomodulation either by using CMV-CTLs or CMVIG, as well as mixed prophylaxis and pre-emptive approaches guided by CMI. The overall profile of the patient, including the IST regimen, D/R serology, risk of rejection, and CMI, will be the source of data to be integrated to accurately predict the risk for CMV infection/disease.

In the context of heart transplant recipients, who with lung transplant recipients are those with the highest risk of CMV infection and disease,[89] CAV remains one of the first indirect effects to be associated with CMV, even in the modern treatment era. Several studies show that recipients with CMV have a higher risk of CAV than patients without CMV,[124] highlighting the need to prevent CMV reactivation to reduce the incidence of long-term adverse events. However, not all data series agree on the association between CAV and CMV,[125] supporting the concept that many potential confounders may interfere with the pathogenic mechanisms linking CAV to CMV (e.g., different cell tropism for different CMV strains, variable interaction between CMV and host immunity).

Finally, the quest for an effective CMV vaccine is ongoing, but the broad range of candidates being investigated could mean that it becomes a clinical option in the future.

In conclusion, discussions during the CMV International Symposium highlighted that management of CMV remains complicated despite advances that have had a substantial benefit on patient outcomes. At an individual level, many patients are still at risk, and management of CMV, when combined with risk of GvHD and complications of therapy, remains a challenge. Luciano Potena reminded delegates to keep patients at the heart of decision making and encouraged ongoing collaboration between allo-HCT and SOT settings to allow the field to continue to advance and to achieve the ultimate goal of slaying the Troll of Transplantation.

AUTHOR CONTRIBUTIONS

All authors (scientific committee and members of the International CMV Symposium faculty) developed content for presentation during the International CMV symposium meeting or moderated sessions where key points reflected in the manuscript were discussed. The scientific committee (Ibrahim Yakoub-Agha, Camille Kotton, Julian Torre-Cisneros) developed the manuscript based on content and discussion points shared during the meeting. All members of the International CMV symposium faculty actively reviewed the manuscript content and approved the manuscript prior to submission.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST STATEMENT

In addition to speaking at the Biotest AG-sponsored International Symposium 2023, the following disclosures/conflict of interest statements are provided:

Ibrahim Yakoub Agha: honoraria from Biotest and MSD; *Camille N Kotton*: Consultant for Abbott Labs, Biotest, Evrys, Hookipa, Merck, Oxford Immunotec, QIAGEN, Roche Diagnostics. *Julián Torre-Cisneros*: Recipient of research grants from Cellestis (a QUIAGEN company), MSD, and Roche. Recipient of educational grants from MSD and Roche. Member of advisory boards for Biotest, MSD and Roche. The research has been supported by CIBER – Consorcio Centro de Investigación Biomédica en Red- (CB 2021), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación and Unión Europea—NextGenerationEU.

The international CMV symposium faculty

Sophie Alain: research grants from Altona, BioMérieux, Biotest, GSK, MSD, Qiagen, and Shire (a Takeda company). Member of the advisory board for the Quality Control for Molecular Diagnostics and Agence nationale de sécurité du medicament et des produits de santé ANSM expert for delivery of anti-CMV for compassionate use in refractory/resistant patients; Reem Almaghrabi: nothing additional to disclose; David Beauvais: honoraria from MSD; Oriol Bestard: Oxford Immunotec; Emily Blumberg: research grants (site investigator) from Merck and Takeda; Udo Boeken: consultant and speaker for Biotest and speaker/advisor for Astellas, Novartis, and Takeda; Roy Chemaly: consultant/speaker advisor for Adagio Therapeutics, ADMA Biologics, AiCuris, Ansun Pharmaceuticals, Astellas, Janssen, Karius, Merck/MSD, Oxford Immunotec, Partner Therapeutics, Pulmotec, Roche/Genentech, Shinogi, Takeda, and Tether. Research grants from AiCuris, Ansun Pharmaceuticals, Eurofins-Viracor, Genentech, Karius, MSD, Oxford Immunotec, and Takeda; Lana Desnica: honoraria received from Biotest, MSD and Takeda; Mario Fernández-Ruiz: speaker for Astellas Pharma, bioMérieux, Gilead Sciences, and MSD; Raffaella Greco: Medac, Pfizer and, Magenta; Paolo Grossi: consultant for Allovir, Biotest, Gilead, MSD, Takeda, and member of speaker's bureau for Atara, Biotest, Gilead, MSD, and Takeda. Nassim Kamar: speaker/advisor for Astellas, AstraZeneca, Biotest, CSL Behring, Chiesi, ExeViR, Hansa, MSD, GSK, Novartis, Sanofi, Sandoz, and Takeda; Hannah Kaminski: speaker for Biotest, consultant for MSD, GSK, and Takeda; Nikolaus Kneidinger: advisor/speaker for CSL Behring, MSD, and Takeda; Guido Kobbe: advisor/speaker for AbbVie, Amgen, Biotest, BMS-Celgene, Eurocept, MSD, Pfizer, and Takeda. Research grants from AbbVie, Amgen, BMS-Celgene, Eurocept, and Medac; Michele Malagola: advisory board member for Biotest and MSD; María E. Martínez-Muñoz: Speaker/advisor for Biotest, Gilead Sciences, and

ORCID

Camille N. Kotton https://orcid.org/0000-0001-7320-2234
Julian Torre-Cisneros https://orcid.org/0000-0003-1529-6302
Ibrahim Yakoub-Agha https://orcid.org/0000-0003-4524-8782

REFERENCES

1. Jorgenson MR, Descourouez JL, Wong C, et al. Cytomegalovirus antiviral stewardship in the COVID-19 era: increasing complexity of prophylaxis and treatment and potential mitigation strategies. *Transpl Infect Dis.* 2021;23(4):e13586.

2. Yamamoto Y, Shiroyama T, Hirata H, et al. Prolonged corticosteroid therapy and cytomegalovirus infection in patients with severe COVID-19. *J Med Virol.* 2022;94(3):1067-1073.

3. Gatto I, Biagioni E, Coloretti I, et al. Cytomegalovirus blood reactivation in COVID-19 critically ill patients: risk factors and impact on mortality. *Intensive Care Med.* 2022;48(6):706-713.

4. Manuel O, Kralidis G, Mueller NJ, et al. Impact of antiviral preventive strategies on the incidence and outcomes of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant.* 2013;13(9):2402-2410.

5. Stern M, Hirsch H, Cusini A, et al. Cytomegalovirus serology and replication remain associated with solid organ graft rejection and graft loss in the era of prophylactic treatment. *Transplantation.* 2014;98(9):1013-1018.

6. Roman A, Manito N, Campistol JM, et al. The impact of the prevention strategies on the indirect effects of CMV infection in solid organ transplant recipients. *Transplant Rev (Orlando).* 2014;28(2):84-91.

7. Chuleerarux N, Thongkam A, Manothummetha K, et al. Does posttransplant cytomegalovirus increase the risk of invasive aspergillosis in solid organ transplant recipients? A systematic review and meta-analysis. *J Fungi (Basel).* 2021;7(5):327.

8. Sen P, Wilkie AR, Ji F, et al. Linking indirect effects of cytomegalovirus in transplantation to modulation of monocyte innate immune function. *Sci Adv.* 2020;6(17):eaax9856.

9. Singh N, Winston DJ, Razonable RR, et al. Effect of preemptive therapy vs antiviral prophylaxis on cytomegalovirus disease in seronegative liver transplant recipients with seropositive donors: a randomized clinical trial. *JAMA.* 2020;323(14):1378-1387.

10. Lowance D, Neumayer HH, Legendre CM, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. *N Engl J Med.* 1999;340(19):1462-1470.

11. Razonable RR, Rivero A, Rodriguez A, et al. Allograft rejection predicts the occurrence of late-onset cytomegalovirus (CMV) disease among CMV-mismatched solid organ transplant patients receiving prophylaxis with oral ganciclovir. *J Infect Dis.* 2001;184(11):1461-1464.

12. Gane E, Saliba F, Valdecasas GJ, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group [corrected]. *Lancet.* 1997;350(9093):1729-1733.

13. Martin-Gandul C, Stampf S, Héquet D, et al. Preventive strategies against cytomegalovirus and incidence of α-herpesvirus infections in solid organ transplant recipients: a nationwide cohort study. *Am J Transplant.* 2017;17(7):1813-1822.

14. Opelz G, Döhler B, Ruhenstroth A. Cytomegalovirus prophylaxis and graft outcome in solid organ transplantation: a collaborative transplant study report. *Am J Transplant.* 2004;4(6):928-936.

15. Chmiel C, Speich R, Hofer M, et al. Ganciclovir/valganciclovir prophylaxis decreases cytomegalovirus-related events and bronchiolitis obliterans syndrome after lung transplantation. *Clin Infect Dis.* 2008;46(6):831-839.

16. Mabilangan C, Preiksaitis JK, Cervera C, University of Alberta Cardiothoracic Transplant Group. Impact of donor and recipient cytomegalovirus serology on long-term survival of heart transplant recipients. *Transpl Infect Dis.* 2019;21(1):e13015.

17. Potena L, Holweg CTJ, Chin C, et al. Acute rejection and cardiac allograft vascular disease is reduced by suppression of subclinical cytomegalovirus infection. *Transplantation.* 2006;82(3):398-405.

18. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation.* 2018;102(6):900-931.

19. Palmer SM, Limaye AP, Banks M, et al. Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: a randomized, controlled trial. *Ann Intern Med.* 2010;152(12):761-769.

20. Fisher CE, Knudsen JL, Lease ED, et al. Risk factors and outcomes of ganciclovir-resistant cytomegalovirus infection in solid organ transplant recipients. *Clin Infect Dis.* 2017;65(1):57-63.

21. Yadav DK, Adhikari VP, Yadav RK, et al. Antiviral prophylaxis or preemptive therapy for cytomegalovirus after liver transplantation?: a systematic review and meta-analysis. *Front Immunol.* 2022;13:953210.

22. Limaye AP, Budde K, Humar A, et al. Letermovir vs valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: a randomized clinical trial. *JAMA.* 2023;330:33-42.

23. Hofmann E, Sidler D, Dahdal S, et al. Emergence of letermovir resistance in solid organ transplant recipients with ganciclovir resistant cytomegalovirus infection: a case series and review of the literature. *Transpl Infect Dis.* 2021;23(3):e13515.

24. Cherrier L, Nasar A, Goodlet KJ, Nailor MD, Tokman S, Chou S. Emergence of letermovir resistance in a lung transplant recipient with ganciclovir-resistant cytomegalovirus infection. *Am J Transplant.* 2018;18(12):3060-3064.

25. Paolucci S, Campanini G, Cassaniti I, et al. Emergence of Letermovir-resistant HCMV UL56 mutant during rescue treatment in a liver transplant recipient with ganciclovir-resistant infection HCMV: a case report. *BMC Infect Dis.* 2021;21(1):994.

26. Valganciclovir 450 mg film-coated tablets. Summary of Product Characteristics. Accessed September 28, 2023. https://www.medicines.org.uk/emc/product/8177/smpc/

27. Rissling O, Naik M, Brakemeier S, et al. High frequency of valganciclovir underdosing for cytomegalovirus prophylaxis after renal transplantation. *Clin Kidney J.* 2018;11(4):564-573.

28. Khoury JA, Storch GA, Bohl DL, et al. Prophylactic versus preemptive oral valganciclovir for the management of cytomegalovirus infection in adult renal transplant recipients. *Am J Transplant.* 2006;6(9):2134-2143.

29. Reischig T, Jindra P, Hes O, Svecová M, Klaboch J, Treska V. Vala-cyclovir prophylaxis versus preemptive valganciclovir therapy to prevent cytomegalovirus disease after renal transplantation. *Am J Transplant.* 2008;8(1):69-77.

30. Kliem V, Fricke L, Wollbrink T, Burg M, Radermacher J, Rohde F. Improvement in long-term renal graft survival due to CMV prophylaxis with oral ganciclovir: results of a randomized clinical trial. *Am J Transplant.* 2008;8(5):975-983.

31. Witzke O, Hauser IA, Bartels M, et al. Valganciclovir prophylaxis versus preemptive therapy in cytomegalovirus-positive renal allograft recipients: 1-year results of a randomized clinical trial. *Transplantation.* 2012;93(1):61-68.

32. Doss KM, Kling CE, Heldman MR, et al. Real-world effectiveness of preemptive therapy (PET) for cytomegalovirus (CMV) disease prevention in CMV high-risk donor seropositive/recipient seronegative (D+R-) liver transplant recipients (LTxR). *Transpl Infect Dis.* 2023;25(2):e14015.

33. Pilch NA, Bowman LJ, Taber DJ. Immunosuppression trends in solid organ transplantation: the future of individualization, monitoring, and management. *Pharmacotherapy.* 2021;41(1):119-131.

34. Kaminski H, Kamar N, Thaunat O, et al. Incidence of cytomegalovirus infection in seropositive kidney transplant recipients treated with everolimus: a randomized, open-label, multicenter phase 4 trial. *Am J Transplant.* 2022;22(5):1430-1441.

35. Kobashigawa J, Ross H, Bara C, et al. Everolimus is associated with a reduced incidence of cytomegalovirus infection following de novo cardiac transplantation. *Transpl Infect Dis.* 2013;15(2):150-162.

36. Eisen HJ, Kobashigawa J, Starling RC, et al. Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. *Am J Transplant.* 2013;13(5):1203-1216.

37. Kaminski H, Marseres G, Yared N, et al. mTOR inhibitors prevent CMV infection through the restoration of functional $\alpha\beta$ and $\gamma\delta$ T cells in kidney transplantation. *J Am Soc Nephrol.* 2022;33(1):121-137.

38. Leserer S, Arrieta-Bolaños E, Buttkereit U, Beelen DW, Turki AT. Combined analysis of early CD4+ T cell counts and CMV serostatus may improve CMV risk assessment after allogeneic hematopoietic cell transplantation. *Cells.* 2021;10(12):3318.

39. Stern L, Withers B, Avdic S, et al. Human cytomegalovirus latency and reactivation in allogeneic hematopoietic stem cell transplant recipients. *Front Microbiol.* 2019;10:1186.

40. Beauvais D, Drumez E, Blaise D, et al. Scoring system for clinically significant CMV infection in seropositive recipients following allogenic hematopoietic cell transplant: an SFGM-TC study. *Bone Marrow Transplant.* 2021;56(6):1305-1315.

41. PREVYMIS 240 mg film-coated tablets. Summary of Product Characteristics. Accessed September 28, 2023. https://www.medicines.org.uk/emc/product/11943/smpc#gref

42. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med.* 2017;377(25):2433-2444.

43. Dwabe S, Hsiao M, Ali A, et al. Real world experience: examining outcomes using letermovir for CMV prophylaxis in high-risk allogeneic hematopoietic stem cell patients in the setting of using T-cell depletion as GVHD prophylaxis. *Transpl Immunol.* 2023;76:101769.

44. Sourisseau M, Faure E, Béhal H, et al. The promising efficacy of a risk-based letermovir use strategy in CMV-positive allogeneic hematopoietic cell recipients. *Blood Adv.* 2023;7(5):856-865.

45. Cassaniti I, Colombo AA, Bernasconi P, et al. Positive HCMV DNAemia in stem cell recipients undergoing letermovir prophylaxis is expression of abortive infection. *Am J Transplant.* 2021;21(4):1622-1628.

46. Chavaz L, Royston L, Masouridi-Levrat S, et al. CMV infection after letermovir primary prophylaxis discontinuation in allogeneic hematopoietic cell transplant recipients. *Open Forum Infect Dis.* 2023;10(4):ofad169.

47. Zamora D, Duke ER, Xie H, et al. Cytomegalovirus-specific T-cell reconstitution following letermovir prophylaxis after hematopoietic cell transplantation. *Blood.* 2021;138(1):34-43.

48. Reusser P, Einsele H, Lee J, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Blood.* 2002;99(4):1159-1164.

49. Einsele H, Reusser P, Bornhäuser M, et al. Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. *Blood.* 2006;107(7):3002-3008.

50. Cho SY, Lee DG, Kim HJ. Cytomegalovirus infections after hematopoietic stem cell transplantation: current status and future immunotherapy. *Int J Mol Sci.* 2019;20(11):2666.

51. Burrows SR, Moss DJ, Khanna R. Understanding human T-cell-mediated immunoregulation through herpesviruses. *Immunol Cell Biol.* 2011;89(3):352-358.

52. Bartelink IH, Belitser SV, Knibbe CAJ, et al. Immune reconstitution kinetics as an early predictor for mortality using various hematopoietic stem cell sources in children. *Biol Blood Marrow Transplant.* 2013;19(2):305-313.

53. Aubert G, Hassan-Walker AF, Madrigal JA, et al. Cytomegalovirus-specific cellular immune responses and viremia in recipients of allogeneic stem cell transplants. *J Infect Dis.* 2001;184(8):955-963.

54. Gerna G, Lilleri D, Fornara C, et al. Monitoring of human cytomegalovirus-specific CD4 and CD8 T-cell immunity in patients receiving solid organ transplantation. *Am J Transplant.* 2006;6(10):2356-2364.

55. Lúcia M, Crespo E, Melilli E, et al. Preformed frequencies of cytomegalovirus (CMV)-specific memory T and B cells identify protected CMV-sensitized individuals among seronegative kidney transplant recipients. *Clin Infect Dis.* 2014;59(11):1537-1545.

56. Greco R, Hoogenboom JD, Bonneville EF, et al. Monitoring for virus-specific T-cell responses and viremia in allogeneic HSCT recipients: a survey from the EBMT Cellular Therapy & Immunobiology Working Party. *Bone Marrow Transplant.* 2023;58(5):603-606.

57. Hall VG, Humar A, Kumar D. Utility of cytomegalovirus cell-mediated immunity assays in solid organ transplantation. *J Clin Microbiol.* 2022;60(8):e0171621.

58. Tassi E, Noviello M, De Simone P, et al. Cytomegalovirus-specific T cells restricted for shared and donor human leukocyte antigens differentially impact on cytomegalovirus reactivation risk after allogeneic hematopoietic stem cell transplantation. *Haematologica.* 2023;108(6):1530-1543.

59. Kaminski H, Jarque M, Halfon M, et al. Different impact of rATG induction on CMV infection risk in D+R- and R+ KTRs. *J Infect Dis.* 2019;220(5):761-771.

60. Jarque M, Crespo E, Melilli E, et al. Cellular immunity to predict the risk of cytomegalovirus Infection in kidney transplantation: a prospective, interventional, multicenter clinical trial. *Clin Infect Dis.* 2020;71(9):2375-2385.

61. Páez-Vega A, Gutiérrez-Gutiérrez B, Agüera ML, et al. Immunoguided discontinuation of prophylaxis for cytomegalovirus disease in kidney transplant recipients treated with antithymocyte globulin: a randomized clinical trial. *Clin Infect Dis.* 2022;74(5):757-765.

62. Fernández-Ruiz M, Rodríguez-Goncer I, Parra P, et al. Monitoring of CMV-specific cell-mediated immunity with a commercial ELISA-based interferon-γ release assay in kidney transplant recipients treated with antithymocyte globulin. *Am J Transplant.* 2020;20(8):2070-2080.

63. Kumar D, Chin-Hong P, Kayler L, et al. A prospective multicenter observational study of cell-mediated immunity as a predictor for cytomegalovirus infection in kidney transplant recipients. *Am J Transplant.* 2019;19(9):2505-2516.

64. Chemaly RF, El Haddad L, Winston DJ, et al. Cytomegalovirus (CMV) cell-mediated immunity and CMV infection after allogeneic hematopoietic cell transplantation: the REACT study. *Clin Infect Dis.* 2020;71(9):2365-2374.

65. El Haddad L, Ariza-Heredia E, Shah DP, et al. The ability of a cytomegalovirus ELISPOT assay to predict outcome of low-level CMV reactivation in hematopoietic cell transplant recipients. *J Infect Dis.* 2019;219(6):898-907.

66. Girmenia C, Lazzarotto T, Bonifazi F, et al. Assessment and prevention of cytomegalovirus infection in allogeneic hematopoietic stem cell transplant and in solid organ transplant: a multidisciplinary consensus conference by the Italian GITMO, SITO, and AMCLI societies. *Clin Transplant.* 2019;33(10):e13666.

67. Valadkhani B, Kargar M, Ashouri A, Hadjibabaie M, Gholami K, Ghavamzadeh A. The risk factors for cytomegalovirus reactivation following stem cell transplantation. *J Res Pharm Pract.* 2016;5(1):63-69.

68. Ljungman P, de la Camara R, Robin C, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis.* 2019;19(8):e260-e272.

69. Riddell SR, Watanabe KS, Goodrich JM, Li CR, Agha ME, Greenberg PD. Restoration of viral immunity in immunodeficient humans by the adoptive transfer of T cell clones. *Science.* 1992;257(5067):238-241.

70. Walter EA, Greenberg PD, Gilbert MJ, et al. Reconstitution of cellular immunity against cytomegalovirus in recipients of allogeneic bone marrow by transfer of T-cell clones from the donor. *N Engl J Med.* 1995;333(16):1038-1044.

71. Withers B, Clancy L, Burgess J, et al. Establishment and operation of a third-party virus-specific T Cell bank within an allogeneic stem cell transplant program. *Biol Blood Marrow Transplant.* 2018;24(12):2433-2442.

72. Withers B, Blyth E, Clancy LE, et al. Long-term control of recurrent or refractory viral infections after allogeneic HSCT with third-party virus-specific T cells. *Blood Adv.* 2017;1(24):2193-2205.

73. Tzannou I, Watanabe A, Naik S, et al. "Mini" bank of only 8 donors supplies CMV-directed T cells to diverse recipients. *Blood Adv.* 2019;3(17):2571-2580.

74. Snydman DR, Werner BG, Heinze-Lacey B, et al. Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal-transplant recipients. *N Engl J Med.* 1987;317(17):1049-1054.

75. Germer M, Herbener P, Schüttrumpf J. Functional properties of human cytomegalovirus hyperimmunoglobulin and standard immunoglobulin preparations. *Ann Transplant.* 2016;21:558-564.

76. Barten MJ, Baldanti F, Staus A, Hüber CM, Glynou K, Zuckermann A. Effectiveness of prophylactic human cytomegalovirus hyperimmunoglobulin in preventing cytomegalovirus infection following transplantation: a systematic review and meta-analysis. *Life (Basel).* 2022;12(3):361.

77. Bonaros N, Mayer B, Schachner T, Laufer G, Kocher A. CMV-hyperimmune globulin for preventing cytomegalovirus infection and disease in solid organ transplant recipients: a meta-analysis. *Clin Transplant.* 2008;22(1):89-97.

78. Hodson EM, Jones CA, Strippoli GFM, Webster AC, Craig JC. Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst Rev.* 2007;(2):CD005129. https://doi.org/10.1002/14651858.CD005129.pub2

79. Opelz G, Daniel V, Naujokat C, Fickenscher H, Döhler B. Effect of cytomegalovirus prophylaxis with immunoglobulin or with antiviral drugs on post-transplant non-Hodgkin lymphoma: a multicentre retrospective analysis. *Lancet Oncol.* 2007;8(3):212-218.

80. Jaksch P, Wiedemann D, Kocher A, Muraközy G, Augustin V, Klepetko W. Effect of cytomegalovirus immunoglobulin on the incidence of lymphoproliferative disease after lung transplantation: single-center experience with 1157 patients. *Transplantation.* 2013;95(5):766-772.

81. Kocher AA, Bonaros N, Dunkler D, et al. Long-term results of CMV hyperimmune globulin prophylaxis in 377 heart transplant recipients. *J Heart Lung Transplant.* 2003;22(3):250-257.

82. Bonaros NE, Kocher A, Dunkler D, et al. Comparison of combined prophylaxis of cytomegalovirus hyperimmune globulin plus ganciclovir versus cytomegalovirus hyperimmune globulin alone in high-risk heart transplant recipients. *Transplantation.* 2004;77(6):890-897.

83. Santhanakrishnan K, Yonan N, Callan P, Karimi E, Al-Aloul M, Venkateswaran R. The use of CMVIg rescue therapy in cardiothoracic transplantation: a single-center experience over 6 years (2011-2017). *Clin Transplant.* 2019;33(8):e13655.

84. Charlotte R, François P, Jonathan M, et al. Use of anti-CMV immunoglobulins in lung transplant recipients: the French experience. *Transpl Infect Dis.* 2021;23(6):e13754.

85. Alsuliman T, Kitel C, Dulery R, et al. Cytotect®CP as salvage therapy in patients with CMV infection following allogeneic hematopoietic cell transplantation: a multicenter retrospective study. *Bone Marrow Transplant.* 2018;53(10):1328-1335.

86. Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant.* 2023;42(5):e1-e141.

87. Avery RK, Arav-Boger R, Marr KA, et al. Outcomes in transplant recipients treated with foscarnet for ganciclovir-resistant or refractory cytomegalovirus infection. *Transplantation.* 2016;100(10):e74-80.

88. Chemaly RF, Chou S, Einsele H, et al. Definitions of resistant and refractory cytomegalovirus infection and disease in transplant recipients for use in clinical trials. *Clin Infect Dis.* 2019;68(8):1420-1426.

89. Natori Y, Humar A, Husain S, et al. Recurrence of CMV infection and the effect of prolonged antivirals in organ transplant recipients. *Transplantation.* 2017;101(6):1449-1454.

90. Gardiner BJ, Nierenberg NE, Chow JK, Ruthazer R, Kent DM, Snydman DR. Absolute lymphocyte count: a predictor of recurrent cytomegalovirus disease in solid organ transplant recipients. *Clin Infect Dis.* 2018;67(9):1395-1402.

91. Åsberg A, Humar A, Rollag H, et al. Lessons learned from a randomized Study of oral valganciclovir versus parenteral ganciclovir treatment of cytomegalovirus disease in solid organ transplant recipients: the VICTOR trial. *Clin Infect Dis.* 2016;62(9):1154-1160.

92. Boivin G, Goyette N, Farhan M, Ives J, Elston R. Incidence of cytomegalovirus UL97 and UL54 amino acid substitutions detected after 100 or 200 days of valganciclovir prophylaxis. *J Clin Virol.* 2012;53(3):208-213.

93. Grossi P, Kamar N, Saliba F, et al. Cytomegalovirus management in solid organ transplant recipients: a pre-COVID-19 survey from the working group of the European Society for Organ Transplantation. *Transpl Int.* 2022;35:10332.

94. Mehta Steinke SA, Alfares M, Valsamakis A, et al. Outcomes of transplant recipients treated with cidofovir for resistant or refractory cytomegalovirus infection. *Transpl Infect Dis.* 2021;23(3):e13521.

95. Khawaja F, Spallone A, Kotton CN, Chemaly RF. Cytomegalovirus infection in transplant recipients: newly approved additions to our armamentarium. *Clin Microbiol Infect.* 2023;29(1):44-50.

96. Papanicolaou GA, Silveira FP, Langston AA, et al. Maribavir for refractory or resistant cytomegalovirus infections in hematopoietic-cell or solid-organ transplant recipients: a randomized, dose-ranging, double-blind, phase 2 study. *Clin Infect Dis.* 2019;68(8):1255-1264.

97. Maertens J, Cordonnier C, Jaksch P, et al. Maribavir for pre-emptive treatment of cytomegalovirus reactivation. *N Engl J Med.* 2019;381(12):1136-1147.

98. Avery RK, Alain S, Alexander BD, et al. Maribavir for refractory cytomegalovirus infections with or without resistance post-transplant: results from a phase 3 randomized clinical trial. *Clin Infect Dis.* 2022;75(4):690-701.

99. Alain S, Feghoul L, Girault S, et al. Letermovir breakthroughs during the French named patient programme: interest of monitoring blood concentration in clinical practice. *J Antimicrob Chemother.* 2020;75(8):2253-2257.

100. Ye L, Qian Y, Yu W, Guo G, Wang H, Xue X. Functional profile of human cytomegalovirus genes and their associated diseases: a review. *Front Microbiol.* 2020;11:2104.

101. Griffiths PD, Boeckh M. Antiviral therapy for human cytomegalovirus. In: Arvin A, Campadelli-Fiume G, Mocarski E, et al., eds. *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis.* Cambridge University Press; 2007. Accessed September 28, 2023. http://www.ncbi.nlm.nih.gov/books/NBK47388/

102. Chou S, Ercolani RJ, Lanier ER. Novel cytomegalovirus UL54 DNA polymerase gene mutations selected in vitro that confer brincidofovir resistance. *Antimicrob Agents Chemother.* 2016;60(6):3845-3848.

103. Marty FM, Winston DJ, Rowley SD, et al. CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. *N Engl J Med.* 2013;369(13):1227-1236.

104. Marty FM, Winston DJ, Chemaly RF, et al. A randomized, double-blind, placebo-controlled phase 3 trial of oral brincidofovir for cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2019;25(2):369-381.

105. Hussein ITM, Brooks J, Bowlin TL. The discovery and development of filociclovir for the prevention and treatment of human cytomegalovirus-related disease. *Antiviral Res.* 2020;176:104710.

106. Chou S. Advances in the genotypic diagnosis of cytomegalovirus antiviral drug resistance. *Antiviral Res.* 2020;176:104711.

107. Oiknine-Djian E, Bar-On S, Laskov I, et al. Artemisone demonstrates synergistic antiviral activity in combination with approved and experimental drugs active against human cytomegalovirus. *Antiviral Res.* 2019;172:104639.

108. Oiknine-Djian E, Weisblum Y, Panet A, Wong HN, Haynes RK, Wolf DG. The artemisinin derivative artemisone is a potent inhibitor of human cytomegalovirus replication. *Antimicrob Agents Chemother.* 2018;62(7):e00288-18.

109. Gokarn A, Shenoy R, Punatar S, et al. Efficacy of artesunate for treatment of cytomegalovirus reactivation post allogeneic haematopoietic stem cell transplants. *Bone Marrow Transplant.* 2023;58(2):209-211.

110. Combs JA, Monk CH, Harrison MAA, et al. Inhibiting cytomegalovirus replication through targeting the host electron transport chain. *Antiviral Res.* 2021;194:105159.

111. Diamond DJ, La Rosa C, Chiuppesi F, et al. A fifty-year odyssey: prospects for a cytomegalovirus vaccine in transplant and congenital infection. *Expert Rev Vaccines.* 2018;17(10):889-911.

112. Anderholm KM, Bierle CJ, Schleiss MR. Cytomegalovirus vaccines: current status and future prospects. *Drugs.* 2016;76(17):1625-1645.

113. Ljungman P, Bermudez A, Logan AC, et al. A randomised, placebo-controlled phase 3 study to evaluate the efficacy and safety of ASP0113, a DNA-based CMV vaccine, in seropositive allogeneic haematopoietic cell transplant recipients. *EClinicalMedicine.* 2021;33:100787.

114. Pass RF, Zhang C, Evans A, et al. Vaccine prevention of maternal cytomegalovirus infection. *N Engl J Med.* 2009;360(12):1191-1199.

115. Bernstein DI, Munoz FM, Callahan ST, et al. Safety and efficacy of a cytomegalovirus glycoprotein B (gB) vaccine in adolescent girls: a randomized clinical trial. *Vaccine.* 2016;34(3):313-319.

116. Griffiths PD, Stanton A, McCarrell E, et al. Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial. *Lancet.* 2011;377(9773):1256-1263.

117. Plotkin SA, Wang D, Oualim A, et al. The status of vaccine development against the human cytomegalovirus. *J Infect Dis.* 2020;221(Suppl 1):S113-S122.

118. A phase 1/2, first-time-in human (FTiH), randomized, observer-blind, placebo-controlled, dose escalation study to assess safety, reactogenicity and immunogenicity of a candidate cytomegalovirus (CMV) vaccine comprising recombinant protein and adjuvant when administered intramuscularly in healthy adults. Clinicaltrials.gov. Accessed September 28, 2023. https://clinicaltrials.gov/study/NCT05089630

119. Aldoss I, La Rosa C, Baden LR, et al. Poxvirus vectored cytomegalovirus vaccine to prevent cytomegalovirus viremia in transplant recipients: a phase 2, randomized clinical trial. *Ann Intern Med.* 2020;172(5):306-316.

120. Nakamura R, La Rosa C, Longmate J, et al. Viraemia, immunogenicity, and survival outcomes of cytomegalovirus chimeric epitope vaccine supplemented with PF03512676 (CMVPepVax) in allogeneic haemopoietic stem-cell transplantation: randomised phase 1b trial. *Lancet Haematol.* 2016;3(2):e87-98.

121. A phase II randomized, placebo-controlled, multicenter trial to evaluate protective function of an optimized dose of CMVPepVax in recipients of an allogeneic hematopoietic stem cell transplant. Clinicaltrials.gov. Accessed September 28, 2023. https://clinicaltrials.gov/study/NCT02396134

122. Sommerer C, Schmitt A, Hückelhoven-Krauss A, et al. Peptide vaccination against cytomegalovirus induces specific T cell response in responses in CMV seronegative end-stage renal disease patients. *Vaccines (Basel).* 2021;9(2):133.

123. Balfour HH. Cytomegalovirus: the troll of transplantation. *Arch Intern Med.* 1979;139(3):279-280.

124. Delgado JF, Reyne AG, de Dios S, et al. Influence of cytomegalovirus infection in the development of cardiac allograft vasculopathy after heart transplantation. *J Heart Lung Transplant.* 2015;34(8):1112-1119.

125. Zakliczyński M, Krynicka-Mazurek A, Pyka Ł, et al. The influence of cytomegalovirus infection, confirmed by pp65 antigen presence, on the development of cardiac allograft vasculopathy. *Transplant Proc.* 2007;39(9):2866-2869.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.